A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

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A Multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

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At a Glance Commentary

Scientific knowledge on the subject

Patients with severe heterogeneous or homogeneous emphysema and hyperinflation selected for little to no collateral ventilation between target and ipsilateral lobe benefit from Zephyr® Endobronchial Valve EBV® treatment with significant clinical improvements over standard of care medical management in lung function, exercise tolerance, dyspnea and quality of life out to 6 months.

What this study adds to the field

This multicenter, prospective, randomized controlled clinical trial of the Zephyr® Endobronchial Valve EBV® treatment in patients with heterogeneous emphysema distribution and little to no collateral ventilation, demonstrates significant clinically meaningful benefits over current standard of care medical therapy in lung function, dyspnea, exercise capacity, and quality of life out to at least 12-months post-procedure.

Author Contributions

Gerard J. Criner, MD: GC is the Principal Investigator of the study and collaborated on design of the study, advised on medical issues during the conduct of the study, actively recruited and treated patients in the study, participated in acquisition of data, analysis and interpretation of the data, and development of the manuscript.

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Brian Armstrong, MS: BA managed the Study Database, oversaw the Database Snapshot and performed and directed all the statistical analyses per the Statistical Analysis Plan, helped with interpretation of the statistics and their inclusion in the manuscript, and reviewed and approved the final manuscript.

Narinder S Shargill, PhD: NS oversaw the trial operations and analysis of the data per the prespecified statistical analysis plan, supported additional analyses requested by the authors and approved of the decision to submit the manuscript for publication.

Dirk-Jan Slebos, MD: DJS is an investigator in the study and actively recruited and treated patients in the study, participated in acquisition of data, helped with interpretation of the data, and provided revisions to the manuscript.

Abstract

Rationale: This is the first multicenter RCT to evaluate the effectiveness and safety of Zephyr® Endobronchial Valve EBV® in patients with little to no collateral ventilation (CV) out to 12-months.

Objectives: To evaluate the effectiveness and safety of Zephyr EBV in heterogeneous emphysema with little to no collateral ventilation in the treated lobe.

Methods: Subjects were enrolled with a 2:1 randomization (EBV: Standard-of-Care (SoC)) at 24 sites. Primary outcome at 12-months was the ΔEBV–SoC of subjects with a post-bronchodilator FEV_1 improvement from baseline of ≥15%. Secondary endpoints included absolute changes in post-BD FEV_1, Six-Minute Walk Distance (6MWD), and St. George's Respiratory Questionnaire (SGRQ) scores.

Results: 190 subjects, 128 EBV and 62 SoC were randomized. At 12-months, 47.7% EBV and 16.8% SoC subjects had a ΔFEV_1 ≥15% ($p<0.001$). ΔEBV–SoC at 12-months was statistically and clinically significant: for FEV_1 (L), 0.106L ($p<0.001$); 6MWD, +39.31m ($p=0.002$); and SGRQ, -7.05 points ($p=0.004$). Significant ΔEBV–SoC were also observed in hyperinflation (RV, -522ml; $p<0.001$), mMRC, -0.8 points ($p<0.001$), and the BODE Index (-1.2 points). Pneumothorax was the most common serious adverse event in the Treatment Period (procedure to 45 days), in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12-months.

Conclusions: Zephyr EBV provides clinically meaningful benefits in lung function, exercise tolerance, dyspnea and quality of life out to at least 12-months, with an acceptable safety profile in patients with little or no collateral ventilation in the target lobe.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of mortality in the United States with 15.4 million physician visits, 1.5 million emergency department visits, and 726,000 hospitalizations each year[1]. Patients with advanced emphysema, one of the diseases that comprises COPD, are characterized by hyperinflation that precipitates breathlessness and predisposes individuals to exacerbations and has a greater negative impact on health status than self-reported cardiovascular disease and diabetes[2,3].

Many surgical procedures have been devised to treat this disease including costochondrectomy, phrenic crush, pneumoperitoneum, pleural abrasion, surgical lung denervation, and thoracoplasty. But apart from Lung Volume Reduction Surgery (LVRS), bullectomy, and lung transplantation all others have not proven to be viable[4]. LVRS has been extensively studied, and in appropriately selected patients reduces hyperinflation improving lung function, dyspnea, exercise tolerance, and long-term survival[5,6,7]. However, LVRS is under-utilized due to concerns about the invasiveness of the procedure, increased associated perioperative morbidity and mortality, and narrow patient eligibility criteria[8,9,10]. Zephyr® Endobronchial Valves (Zephyr® EBV®, Pulmonx Corporation, Redwood City, CA) are small duckbill valves inserted bronchoscopically into the lung to occlude an emphysematous lobe. Lobar deflation from the EBV leads to partial or full lobar atelectasis, thus reducing hyperinflation and mimicking the mechanisms of LVRS.

In the first randomized controlled trial of Zephyr EBV the “Endobronchial Valve for Emphysema Palliation Trial” (VENT), the co-primary endpoints of forced expiratory

volume in 1 second (FEV_1) and Six-Minute Walk Distance (6MWD) achieved statistical but not clinically meaningful improvements between groups[11]. Post-hoc analysis showed that only patients with complete fissures in the treated lung and in whom lobar occlusion (occlusive positioning of valves in all segmental and sub-segmental airways feeding the target lobe) was achieved had clinically meaningful outcomes[12,13].

Following VENT, subsequent short-term studies with Zephyr EBV have shown that by selecting patients with little to no collateral ventilation between target and ipsilateral lobes and performing post-procedure confirmation of lobar occlusion, similar benefits to LVRS can be achieved in patients with heterogeneous or homogeneous emphysema[14,15,16,17] but with less morbidity. All these studies included a control arm and followed subjects out to three or six months.

LIBERATE is the first large randomized controlled multicenter international study conducted in patients with severe heterogeneous emphysema and with little to no collateral ventilation in the target lung to evaluate the effectiveness, safety and durability of benefit out to 12-months. The study compared Zephyr EBV treatment with standard medical management to standard medical management alone.

Footnote: Some of the results have been previously reported in the form of an Abstract[18].

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Methods

This trial (NCT01796392) conducted under a U.S. Food and Drug Administration approved Investigational Device Exemption for the Zephyr Endobronchial Valve (EBV) enrolled patients between October 2013 and September 2016 at 24 sites (18 sites in the United States and 6 sites outside the United States. The study was approved by the respective Institutional Review Boards or Ethics Committees at each site and all participating subjects provided written informed consent. The consent informed all subjects that their final enrollment in the study would be determined following the bronchoscopy procedure for collateral ventilation assessment with the Chartis® Pulmonary Assessment System (510K Cleared K111764; Pulmonx Corporation, Redwood City, CA).

The sample size was estimated using the results from the VENT Trial (US and European cohorts)[11, 12]. Based on the results of these studies, the responder rate (FEV_1 improvement of ≥15%) in the Zephyr EBV treatment group was expected to be approximately 35% at 1 year. The responder rate for the control group was not expected to exceed 10% at 1 year. Assuming a two-sided 0.05 alpha level, study power of 90%, and 2:1 allocation random assignment, a sample size of 147 was expected to be adequate to test for superiority. The study sample size was increased to 183 to allow for 20% lost to follow-up and incomplete data. Each study site will be allowed to enroll a maximum of 25 study participants.

Eligible emphysema patients were ex-smokers between 40 and 75 years of age, with post-bronchodilator FEV_1 (post-BD FEV_1) of between 15% and 45% predicted, total lung capacity (TLC) >100% predicted, residual volume (RV) ≥175% predicted, DLCO ≥20%

predicted, and a 6-minute walk distance (6MWD) between 100m and 500m following a supervised pulmonary rehabilitation program (complete Inclusion and Exclusion criteria provided in Section E1 in the online supplement). Target lobe selection was based on a >50% destruction score (percentage of voxels < -910 Hounsfield units on CT) and heterogeneous emphysema defined as absolute difference of 15 or greater in destruction scores between the targeted and ipsilateral lobes determined by investigational sites using Myrian® quantitative software (Intrasense - Montpellier, France; Figure E1 in the online supplement).

Eligible patients were assessed with the Chartis to determine collateral ventilation status between targeted and adjacent lobes before randomization[19] (additional details provided in section E2 in the online Supplement). Figure E2 in the online supplement shows examples of “collateral ventilation negative” and “collateral ventilation positive” assessments on Chartis. Subjects deemed to have a “collateral ventilation negative” target lobe by Chartis were randomized in a 2:1 fashion (blocked design) immediately after the Chartis assessment to either the EBV or Standard-of-Care (SoC) groups (section E3 in the online supplement). The bronchoscopy procedure for subjects randomized to SoC was terminated after the Chartis assessment and subjects recovered per institutional clinical practice. Subjects randomized to EBV underwent placement of Zephyr EBV valves during the same session with the intent to achieve complete lobar occlusion[20]. Subjects assessed as “collateral ventilation positive” were exited from the Study. See Sections E2 in the online supplement for complete details.

Subjects randomized to SoC were discharged after post-bronchoscopy recovery. Subjects randomized to EBV were hospitalized for 5 nights regardless of clinical status

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and underwent daily chest x-rays (with the first taken within an hour of the bronchoscopy procedure) until discharge (see Figure E3 in the online supplement for post-randomization follow-up of study subjects). Frequency of chest x-rays for any hospitalization for an adverse event was at the discretion of the physician, but a chest x-ray was required on the day of discharge. Clinical staff was trained regarding the risk of a pneumothorax; equipment needed to treat a pneumothorax was kept bedside. At discharge, subjects were provided a wrist-band denoting "patient at risk of pneumothorax" and were instructed to seek immediate medical attention in the event of symptoms of a potential pneumothorax. EBV subjects were contacted daily by phone for 10 days after discharge; and evaluated during site visits at Day 7, Day 30 and Day 45 after discharge. At 45-days, a HRCT scan was performed and assessed by an Independent Core Lab (MedQIA, Los Angeles, CA) to determine Target Lobe Volume Reduction (TLVR), and to verify whether complete lobar occlusion had been achieved. If necessary (TLVR <50%, and incomplete lobar occlusion), a repeat bronchoscopy and valve revision/replacement was recommended. All subjects had clinical visits at 45-day, 3-, 6-, 9- and 12-month post-bronchoscopy. To reduce variability in the collection of the spirometry data, all study sites utilized the ERT MasterScope (eReserarch Technology, Philadelphia, PA), a central diagnostic station attached to a spirometer to capture the FEV_1 and FVC measurements (see section E4 in the online supplement). EBV treated subjects are planned for annual follow-up for an additional 4-years. Following the 12-month evaluation, if eligible, SoC group subjects were given the option to crossover to EBV treatment with planned follow-up for an additional 5 years.

Primary outcome: The primary endpoint was the percentage of subjects in the EBV group at 1-year post-procedure who had an improvement in the post-bronchodilator

(post-BD) FEV_1 of ≥15% compared to the percentage of subjects achieving this improvement in the SoC group.

Secondary outcomes: Difference between EBV and SoC groups in the absolute change at 1 year in FEV_1, St. George's Respiratory Questionnaire (SGRQ) and 6MWD. Additional effectiveness measures included TLVR at 45-days and 1-year post-procedure, Residual Volume (RV), Inspiratory Capacity (IC), Total Lung Capacity (TLC), Functional Residual Capacity (FRC), Diffusing Capacity (DLCO), modified Medical Research Council Dyspnea Scale (mMRC), BODE Index, and for the EBV group only, the absolute and percent change in, and the percentage of subjects achieving a TLVR MCID of ≥350mL[19] relative to Baseline.

Safety was assessed in the Treatment Period (procedure through 45 days) and Longer-Term Period (46 days through one year) through review of all adverse events solicited at all scheduled or unscheduled visits. An independent Clinical Events Committee (CEC) adjudicated serious adverse events (SAE's), device-related events, and select respiratory adverse events. A Data and Safety Monitoring Board (DSMB) provided study oversight to ensure patient rights and safety were respected and maintained.

Statistical Analyses: All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary NC). The rationale for the sample size is provided in section E5 in the online supplement. Descriptive statistics included means, standard deviations and 95% confidence intervals. Continuous variables were compared with an analysis of covariance with the respective Baseline value as the covariate, and categorical variables were compared with the Fisher's Exact test, a Chi-square test, or a Cochran-

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Mantel-Haenszel test. Adverse event rates were compared using Poisson Regression. An interim analysis was performed when 74 subjects had completed 12-month follow-up. To account for the interim analysis, the threshold for significance for the Z-statistic at 12-months was Z≥2.004. The Hochberg step-up procedure was used to control for multiple secondary endpoint analyses[21]. Additional details are provided in Section E6 in the online supplement.

Results

Demographics

One hundred and ninety subjects who met the inclusion/exclusion criteria and were "collateral ventilation negative" for the target lobe according to Chartis assessment were randomized; 128 subjects (56 male/72 female) to EBV, and 62 subjects (33 male/29 female) to SoC (see CONSORT diagram, Figure 1). Both groups were well matched for all Baseline demographics and clinical characteristics, except for the GOLD Stage classification, with more GOLD Stage IV subjects in the SoC group (p=0.037). See Table 1 and Tables E1 through E5 in the online supplement.

Figure 1 about here

Table 1 about here

Procedural Details

A median of 4 valves (range 2 to 8) per subject were implanted in the 128 EBV subjects either under general anesthesia (64.8%) or conscious sedation (35.2%). Distribution of treated lobes was 66.4% left upper lobe, 11.7% left lower lobe, 10.9% right upper lobe, 6.3% right upper and right middle lobe combined, and 4.7% right lower lobe (see Table E6 in the online supplement for procedural details). Sixteen subjects (12.5%) with incomplete lobar occlusion and TLVR <50% verified through the HRCT-assessment at 45-days were eligible for valve adjustment; an additional 2 subjects were considered for valve adjustment by the Investigator. Of these, 11 subjects underwent valve-adjustment procedures (Table E7 in the online supplement). A total of 35 subjects underwent 54 secondary procedures of which 11 procedures were for the protocol allowed adjustment following verification of lobar occlusion, 28 procedures were for valve removals and/or subsequent valve replacement following an adverse event (adverse events requiring

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valve removal included 12 pneumothorax, 2 increased dyspnea, 1 respiratory failure, 1 hypoxemia, 1 subcutaneous emphysema, and 1 valve migration), 12 procedures were for clinical investigation (5 for inspection of valves due to loss of atelectasis, 3 for lavage to clear mucus, 4 to investigate blood in sputum), and the remaining 3 procedures were for patient-requested valve removals for perceived lack of benefit. Eight (8) subjects had all valves removed prior to the 12-month evaluation.

Outcomes

Primary outcome: At 12-months post-procedure, 47.7% of the EBV subjects compared to 16.8% SoC subjects had a ≥15% increase over Baseline in post-BD $FEV_{1,}$ with a between group absolute difference of 31.0 [95% CI: 18.0% to 43.9%; p<0.001; Intention-to-Treat]. The results of the primary effectiveness endpoint are shown graphically in Figure 2.

Figure 2 about here

Secondary outcomes: All 3 secondary endpoints improved in favour of EBV and met statistical significance (Table 2 and Figure 3); the difference of means between EBV and SoC groups from Baseline to 12-months for the absolute change in FEV_1 (L) was 0.106L (17.6% for percent change in FEV_1 (L)) (p<0.001; Figure 3a), 6MWD was 39.3 meters (p=0.002; Figure 3b), and SGRQ was -7.05 points (p=0.004; Figure 3c). Improvements in FEV_1, 6MWD, and SGRQ score following EBV treatment were evident as early as 45 days post-procedure and persisted out to at least 12-months (Figure 4).

Table 2 about here

Figure 3 about here

Figure 4 about here

There were 2 measures at Baseline that were imbalanced between the EBV and SoC groups at a two-sided 0.10 level, mMRC (p=0.091) and GOLD Stage classification based on the percent predicted FEV_1 (p=0.037); however, there was no imbalance between groups based on FEV_1 (L). The interaction term from logistic regression or from analysis of covariance (ANCOVA) with factors of treatment group and Baseline value for mMRC or GOLD Stage classification as covariate were not significant for the primary endpoint (p=0.799 and p=0.906, respectively), or any of the secondary endpoints. Thus, neither of these variables had an impact on the primary or secondary effectiveness endpoints. The p-value for the logistic regression with factors of treatment group, investigational site, and treatment group by investigational site interaction did not show any investigational site effect (p=0.785).

A significantly greater percentage of subjects in the EBV group compared to the SoC group met or exceeded the MCID for FEV_1 (change of ≥15% and ≥12%), SGRQ (change of ≤ -4 points) and 6MWD (change of ≥25 meters), indicating meaningful clinical benefit was achieved (Figure 5; 6-month responder data in Figure E4 in the online supplement). Correspondingly, a higher percentage of subjects in the SOC group consistently either declined or had no change as compared to the EBV group across these endpoints (Figure 6). Individual subject responses to each of these measures are presented graphically in Figure E5 in the online supplement).

Figure 5 about here

Figure 6 about here

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At 45 days post-procedure, 79.1% of subjects achieved a TLVR of ≥350ml, with a mean reduction of 1.03 ± 0.68L ($p<0.001$) and at 12-months, 84.2% of subjects achieved a TLVR of ≥350ml, with a mean reduction of 1.14 ± 0.70L ($p<0.001$, Figure 5).

Consistent with a durable TLVR at 12-months in the EBV group, there was a significant reduction in hyperinflation as measured by RV (decrease of 522 mL, $p<0.001$; EBV – SoC) and RV/TLC ratio (decrease of 0.05, $p<0.001$; EBV – SoC) (Table 2). At 12-months, RV decrease of 310 ml or more was achieved by 61.6% EBV subjects compared to 22.4% subjects in the SoC group (Figure 5). There was a significant improvement in gas exchange in the EBV compared to SoC groups (increase in DLCO of 0.870 mL CO/min/mm Hg, $p=0.013$; EBV – SoC). The mMRC Dyspnea score improved in favor of EBV with a between group change of -0.8 points ($p<0.001$) with a greater number of subjects in the EBV group (47.8%) compared to the SOC group (18.6%) meeting or exceeding the MCID of -1 points change, $p< 0.001$). Subjects in the EBV group had a greater reduction from Baseline in the multicomponent composite BODE Index as compared to the SoC group, with a mean difference between groups of -1.2 points ($p<0.001$) at 12-months. More subjects in the EBV compared to the SoC group were responders achieving a MCID change of -1 points or less (58.0% vs 24.1%, respectively, $p<0.001$, Figure 6). Supplemental oxygen usage at 12-months in the EBV and SoC group subjects was evaluated to compare change in oxygen usage from Baseline. A larger proportion of EBV subjects compared to SoC (15.7% versus 6.9%, respectively) used less oxygen whereas a larger proportion of SoC subjects compared to EBV (22.4% versus 11.3%, respectively) used more oxygen at 12-months as compared to their Baseline usage; the distribution of oxygen change categories was

statistically significantly (p=0.019) when comparing EBV to SoC (Table E8 in the online supplement).

Subgroup Analyses

Subjects with no valves at 12-month evaluation: Eight subjects who had all valves removed prior to their 12-month evaluation (5 for a pneumothorax, 2 for increased dyspnea, and 1 for pneumonia) did not achieve any benefit when compared to EBV subjects with valves (Table E9 in the online Supplement). Outcomes for subjects with no valves at 12-months were not dissimilar from the SoC group (Table 2).

Type of anesthesia used: The percent of subjects achieving an FEV_1 improvement of ≥15% based on the type of anesthesia used for the EBV procedure were similar with 49.2% in the conscious sedation group and 46.9% in the general anesthesia group. Adverse events occurring at a frequency of 3% or greater for the subgroups of anesthesia type are provided in Table E10 of the online supplement.

Upper versus lower lobe treatments: Similar benefits were seen in the upper lobe and lower lobe subgroups with 45.9% upper lobe treated subjects and 57.1% lower lobe treated subjects with an FEV_1 improvement of ≥15%. The secondary endpoint results for these subgroups are provided in online supplement Table E11.

Adverse events

A summary of all adverse events occurring at a frequency of 3% or more is provided in Table E12 in the online supplement). Of the 501 EBVs which were implanted, 2 EBVs (in 2 subjects) were expectorated and 3 EBVs (in 3 subjects) migrated throughout the

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12-month follow-up for a 0.4% expectoration rate and 0.6% migration rate. Investigator reported respiratory serious adverse events listed in Table 3 show that significantly more subjects in the EBV group (35.2%) compared to the SoC group (4.8%) experienced respiratory serious adverse events (SAEs) in the Treatment Period (day of procedure/randomization to 45 days) immediately following the bronchoscopy procedure ($p<0.001$). This difference was primarily due to a higher frequency of pneumothoraces in the EBV group during the Treatment Period which were managed according to previously published and protocolized pneumothorax management algorithm[22] (Figure E6 in online supplement). Select respiratory serious adverse events with onset following the most recent bronchoscopy procedure are summarized in online supplement Table E13.

However, during the Longer-Term Period (>46 days till 12-month visit), the frequency of events was comparable between groups with 33.6% of the EBV group subjects and 30.6% of the SoC group subjects experiencing one or more respiratory SAEs. During the Longer-Term period (Table 3), there was a lower frequency of SAE's; COPD exacerbations, pneumonias and respiratory failure, in the EBV group as compared to the SoC group with (23.0% vs. 30.6%, 5.7% vs 8.1%, and 0.8% vs 3.2%) respectively, though none of these three frequencies reached statistical significance. Over the 12-month follow-up, there were no episodes of hemoptysis (defined as >200 mL blood loss in <24 hours).

Table 3 about here

Table 4 shows the rates of respiratory SAEs i.e., annualized rates based on the time of occurrence. Investigator reported event rates are compared to the CEC adjudicated event rates; CEC adjudication removed any Investigator bias on nomenclature and

attribution of adverse events by using standardized definitions. Based on the CEC adjudication, during the Treatment period, only the pneumothorax rate was significantly different between groups with 0.275 events/45 days in the EBV group as compared to no events in the SoC group ($p < 0.001$). During the Longer-Term period, CEC adjudicated pneumothorax rates continued to be significantly different between groups with 0.074 events/year compared to no events in the SoC group ($p=0.013$). However, during the Longer-Term period, serious COPD exacerbations and respiratory failure events rates trended to be lower in the EBV group as compared to the SoC group with 0.352 events/year compared and 0.573 events/year ($p=0.053$) and 0.019 events/year compared to 0.099 events/year ($p=0.033$), respectively.

Table 4 about here

Pneumothorax

The major post-procedural complication was pneumothorax with 46 pneumothorax events occurring in 44 EBV subjects (34.4%) during the 12-month period. Eight of these events did not require any intervention (observation only). Thirty eight of the 46 pneumothoraces (83%) were managed with a placement of a chest tube; 12 of these events also required the removal of at least one valve. None of the pneumothoraces occurring in the Longer-term period required the removal of any valves for their management. Forty-three of the 46 pneumothoraces occurred within 13 days of a recent bronchoscopy procedure, of which, 35 (76%) occurred within the first 3 days as shown in Figure 7, for a median event onset time of 1.0 day from a recent bronchoscopy procedure.

Subjects with pneumothorax (n=44) experienced similar benefits at 12-months to subjects without a pneumothorax (n=84); Table E14 in the online supplement.

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Exploratory analyses of subjects who experienced either a “complex” pneumothorax (defined by either death or removal of all EBVs) or a “simple” pneumothorax (all other pneumothoraces) showed that subjects were at higher risk of a “complex” pneumothorax if the lobe with maximum destruction score is not treated, and the non-treated contralateral lung destruction score is >60%. Qualitative assessment of CTs of the EBV group by an independent thoracic radiologist (Imaging Core Lab) of radiological features that included presence or absence of pleural adhesions, intra-parenchymal scars, blebs, bullae, and paraseptal cysts in target and non-target lobes did not identify any variable that was statistically significant in predicting the occurrence of a pneumothorax.

Figure 7 about here

Mortality

During the Treatment Period, there were 4 deaths in the EBV group (3.1% of subjects; 3 from a pneumothorax on Day 3, Day 3 and Day 13, and one from respiratory failure on Day 11) compared to none in the SoC group. The 3 pneumothorax-related deaths occurred in subjects who were not treated in the most diseased lobe. Of the 4 deaths in the EBV group, 3 were considered “definitely related” and one “probably related” to the EBV treatment. During the Longer-Term Period, there was one death (0.8%) in the EBV group on Day 147 resulting from a COPD exacerbation that was not related to the device, and one cardiac arrhythmia related in the SoC group (1.6%) on Day 141.

Discussion

Bronchoscopic lung volume reduction with Zephyr EBV is a breakthrough approach for reducing hyperinflation in patients with severe emphysema. This multicenter RCT demonstrates that Zephyr EBV treatment in severe emphysema patients selected for

little to no collateral ventilation between the treated and the ipsilateral lobe resulted in significant lobar volume reduction, with consequent reduction in hyperinflation, and clinically meaningful improvements in dyspnea, lung function, exercise-capacity and quality of life. Similar results have been reported previously[14,15,16,17].

Except for a higher proportion of categorically defined GOLD Stage IV subjects in the SoC group, the EBV and SoC groups were well matched for Baseline demographics and clinical characteristics; including mean post-bronchodilator FEV_1. However, this difference did not impact either the primary or secondary effectiveness outcomes based on analysis of covariance with Baseline GOLD Stage as a covariate.

The study met its primary endpoint with 47.7% EBV subjects compared to 16.8% SoC subjects achieving an improvement in FEV_1 of ≥15% ($p<0.001$). While the MCID cut off for change in FEV_1 is highly variable, ranging from 10-15%[23], this threshold of 15% for the responder analysis was based on discussion with the FDA as the a priori threshold that they required for the pivotal US trial. The absolute difference in means for FEV_1 of 0.106 L signifies a meaningful important clinical change[24].

Importantly, 79.1% of patients in the EBV group achieved the MCID for TLVR at 45 days; and 84.2% at 12-months confirming proper patient selection with Chartis and successful lobar occlusion. The overall mean change in target lobe volume radiographically determined by HRCT at 12-months was a reduction of 1.14L that corresponded to a mean reduction in residual volume of 0.5L (or a 10.38% decrease from Baseline). TLVR and consequent reduction in residual volume are consistent with

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the proposed mechanism of action of EBV and are comparable to changes following LVRS[25].

The major significant side effect associated with the EBV procedure in the short-term Treatment Period was pneumothorax. Targeted lobar deflation likely causes inflation of the ipsilateral lobe, which can result in a tear of the already compromised parenchymal tissue of the emphysematous ipsilateral lobe, resulting in a pneumothorax. As seen in this study and reported previously[26,]17 subjects experiencing a pneumothorax attained the same level of benefit over the long-term as those without pneumothorax. The 3 pneumothorax-related deaths which occurred in subjects that were not treated in the most diseased lobe due to the heterogeneity requirement (difference in heterogeneity score of 15 between target and ipsilateral lobes) and the absence of collateral ventilation may imply that subjects with reduced capacity in the non-treated contralateral lung experience higher risk from the insult of single-lung ventilation during the pneumothorax event. Physicians performing EBV treatment must be trained on appropriate patient and lobe selection for treatment and anticipate and recognize a pneumothorax which can be readily managed using standard approaches[22].

The difference between groups for the change from Baseline to 12-months of 39 meters in the 6MWD is meaningful and demonstrates the persistent benefit EBV treatment provides in improving exercise tolerance in this patient group [27, 28, 29]. The absolute mean change in 6MWD in the EBV group at 12-months compared to Baseline was only 13 meters. However, left untreated, the decline in 6MWD in COPD patients at GOLD Stage III/IV would be expected to be significant over time[30]. As an example, in the NETT study untreated control patients in the non-high-risk group showed declines of 40

meters in the 6MWD at one year[5]. In this study, the 6MWD in the SoC group declined by -26.3 meters from Baseline to 12-months. While there was a wide range of Baseline 6MWD, there was no correlation between Baseline 6MWD and key outcomes of FEV_1, 6MWD or SGRQ in contrast to NETT where substantial benefit was seen only in patients with low exercise tolerance[31]. Though not powered to demonstrate this change, there was a reduction in the rate of respiratory failure events (p=0.033) and a trend for a reduction in COPD exacerbations resulting in hospitalizations (p=0.053) and in the Longer-Term Period between EBV and SoC. These improvements resulting from a reduction in hyperinflation and improved lung function are consistent with similar findings following LVRS and warrant further study[32].

While prior randomized clinical trials of BLVR with Zephyr EBV treatment demonstrated improvements in lung function, exercise capacity, dyspnea and quality of life compared to controls over a short-term period of 6-months, the LIBERATE Study is the first trial to evaluate these outcomes compared to a control group over a longer period of at least 12-months while reinforcing the suitability of Zephyr EBV for both upper and lower lobe disease, and a wider range of baseline lung function (<20% as compared to NETT) and baseline exercise tolerance. An additional important outcome in LIBERATE is the strong signal for the potential to reduce respiratory failure and COPD exacerbations requiring hospitalization in the Longer-Term, both being important goals of therapy for these patients. Taken together with the previous demonstration of its effectiveness in patients with both heterogeneous[14,15,17] and homogeneous[15,16] emphysema selected for little to no collateral ventilation, unilateral EBV treatment now provides a viable treatment option for a group of emphysema patients that is currently lacking. Unlike surgery or other

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bronchoscopic interventions [33, 34, 35, 36] EBVs are readily removable, allowing the procedure to be reversed if a patient does not respond or has complications.

The 27% frequency of pneumothorax SAE's in the Treatment Period is consistent with previous studies[16,17] and the occurrence of pneumothorax does not appear to negatively impact clinical outcomes as seen in this study and previously reported by Gompelmann et al[26] and Kemp et al[17]. Seventy-six percent (76%) of the pneumothoraces occurred within 3 days following the most recent bronchoscopy (Index procedure for those who did not have a secondary bronchoscopy), and 85% were within 5 days following the most recent bronchoscopy procedure. These statistics support a minimum 3-day hospital stay following EBV procedure to ensure timely management of a pneumothorax if it occurs. As in previous studies, the specific algorithm for managing pneumothorax after EBV procedures developed by experts[22] was used to manage this consequence of the procedure during the present study and highlights the need for physicians performing this procedure to have expertise in the management of procedural complications. One pneumothorax-related death at 13 days post-EBV procedure underlines the need to provide patients with clear instructions on recognizing symptoms of a pneumothorax and to seek emergent help if experiencing these symptoms.

The study has certain limitations. Firstly, while many subjects did not meet the very strict inclusion/exclusion criteria that included baseline lung function measures, prior medical history etc., 40% (280/706) of the screen failures were related to destruction score and heterogeneity requirements, the thresholds for which were arbitrarily chosen at the time the study was designed. Subsequent experience with homogenous patients in other trials[15,16] have established the applicability of this therapy to a broader

population. Similarly, the inclusion of subjects with little or no collateral ventilation was limited to their assessment with Chartis which uses physiological measures of airflow and airway resistance for assessing collateral ventilation status. The more recent evolution of novel Quantitative CT (QCT) techniques now enables the non-invasive screening of subjects for collateral ventilation, with immediate exclusion of subjects with <80% complete fissure on QCT, Chartis requirement only in subjects with >80% to <95% complete fissure on QCT, and treatment with EBV of subjects with >95% complete fissure on QCT without Chartis[37],[38].This approach could have streamlined the screening out of subjects with completely absent fissures and perhaps reduced some screening bronchoscopies in this study. A second limitation of the study was allowing a repeat bronchoscopy for valve revision/replacement only in subjects with TLVR <50%, and incomplete lobar occlusion based on the at 45-day CT assessment by the Imaging Core Lab. These dual criteria were too restrictive and prevented many subjects from potentially benefitting from a revision procedure. In clinical practice[20] repeat bronchoscopies for valve revision are performed based on clinical judgment if a patient has a lack of clinical response or experiences a sudden late loss of benefit.

The observed benefit to risk profile of EBV treatment must be assessed considering the limited treatment options for patients with severe emphysema. LIBERATE shows improvements over non-treated controls at the same magnitude as those seen after LVRS[9] (EBV vs LVRS: FEV_1: 17% vs 19%[32]; 6MWD[5]: 39.3m vs 44.7m; SGRQ score[9]: -7.05 points vs -13.9 points); However, Zephyr EBV treatment has less morbidity compared to LVRS; pneumothorax requiring chest tube (EBV vs LVRS: <30% vs >90%), respiratory failure (EBV vs LVRS: <30% vs >90%), pneumonia (EBV vs LVRS: 4% vs 18%). Specifically, 90-day mortality after EBV is lower than LVRS with a rate of

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3.1% compared to 5.0% in the LVRS non-high-risk group[39]. Although the risks associated with LVRS are considered acceptable, this approach remains relatively under-utilized[40]. The only other remaining alternative of lung transplantation has a limitation of strict patient eligibility superimposed over the limited availability of donor lungs[41].

Conclusion

Zephyr EBV treatment in carefully selected patients with little or no collateral ventilation in the target lobe provides clinically meaningful and statistically significant benefits in lung function, exercise tolerance, dyspnea and quality of life over current standard of care medical therapy out to at least 12-months. The benefits are comparable to those seen with LVRS but with a reduction in post-procedure morbidity. Bronchoscopic lung volume reduction with the Zephyr EBV provides a viable treatment option for patients with severe emphysema and hyperinflation.

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Additional contributions: Safety oversight of the Study was provided by a Data and Safety Monitoring Board (DSMB) comprising of Robert Wise, MD (Chair), Malcolm DeCamp, MD, and Daniel Bloch, PhD (Statistician). The Clinical Events Committee (CEC) adjudicating adverse events included Christopher Cooper, MD (Chair), Sanjay Sethi, MD, Neil McIntyre, MD, and Jeffery Golden, MD.

Disclosures

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Table 1: Baseline Demographics and Clinical Characteristics

Variable	EBV (n=128)	SoC (n=62)	t-test p-value
Gender	56 Males (43.8%) 72 Females (56.3%)	33 Males (53.2%) 29 Females (46.8%)	NS
Age (years)	64.0 ± 6.85	62.5 ± 7.12	NS
BMI (kg/m^2)	24.67 ± 3.90	24.32 ± 4.38	NS
Smoking history (pack years)	50.78 ± 26.88	48.59 ± 28.48	NS
Race White Black/African American Other	 117 (91.4%) 8 (6.3%) 3 (2.3%)	 57 (91.9%) 3 (4.8%) 2 (3.2%)	
Clinical Characteristics			
GOLD Stage	Stage III: 54 (42.2%) Stage IV: 74 (57.8%)	Stage III: 16 (25.8%) Stage IV: 46 (74.2%)	0.037
Emphysema score of the target lobe at -910 HU*	70.9 ± 8.52	70.9 ± 8.77	NS
Heterogeneity Index between target and ipsilateral lobe(s) †	25.5 ± 9.85	26.1 ± 9.81	NS
Post-BD Forced Expiratory Volume in 1 sec. (FEV_1) (L)	0.76 ± 0.25	0.75 ± 0.22	NS
Post-BD Forced Expiratory Volume in 1 sec. (FEV_1) (% predicted)	28.0 ± 7.45	26.2 ± 6.28	NS
Post-BD Forced Expiratory Volume (FVC) (L)	2.60 ± 0.86	2.63 ± 0.79	NS
Post-BD Forced Expiratory Volume (FVC) (% predicted)	71.2 ± 15.99	68.5 ± 13.59	NS
Post-BD FEV_1 /FVC Ratio	0.30 ± 0.06	0.29 ± 0.06	NS
DLCO (mL CO/min/mmHg)	8.53 ± 3.48	8.34 ± 2.70	NS
DLCO (% predicted)	34.6 ± 11.34	33.1 ± 9.84	NS
Residual Volume (L)	4.71 ± 1.05	4.76 ± 0.90	NS
Residual Volume (% predicted)	224.5 ± 42.45	224.6 ± 38.86	NS
Total Lung Capacity (L)	7.54 ± 1.59	7.63 ± 1.37	NS
Total Lung Capacity (% predicted)	133.5 ± 21.17	130.2 ± 12.44	NS
RV/TLC Ratio	0.63 ± 0.09	0.63 ± 0.07	NS
Inspiratory Capacity (IC; L)	1.81 ± 0.70	1.78 ± 0.70	NS
IC/TLC Ratio	0.24 ± 0.07	0.23 ± 0.07	NS

Vital Capacity (L)	2.74 ± 0.9	2.88 ± 0.9	NS
PaO_2 (mmHg)	68.7 ± 11.62	67.8 ± 11.72	NS
$PaCO_2$ (mmHg)	40.1 ± 4.91	41.3 ± 5.33	NS
6 Minute Walk Distance (m)	311 ± 81	302 ± 79	NS
SGRQ Total Score ‡	55.15 ± 14.08	53.10 ± 14.14	NS
mMRC Score §	2.4 ± 0.97	2.2 ± 0.83	NS
BODE Index **	5.34 ± 1.52	5.32 ± 1.56	NS††
COPD Assessment Test (CAT)	19.2 ± 6.32	19.3 ± 6.35	NS
Patients on Continuous Oxygen Usage	46 (35.9%)	17 (27.4%)	NS
Hospital admissions in the last year prior to Screening			
For Respiratory Failure	0.4 ± 0.65	0.3 ± 0.52	
For Pneumonia	0.2 ± 0.38	0.2 ± 0.39	
For COPD Exacerbation	0.4 ± 0.48	0.3 ± 0.44	

Values are means ± standard deviation

* Emphysema destruction score was assessed as the percentage of voxels of less than −910 Hounsfield units on CT.

† Heterogeneity Index was assessed as the difference in the Emphysema score between the target and the ipsilateral lobe.

‡ SGRQ (St. George's Respiratory Questionnaire) scores range from 0 to 100, with higher scores indicating worse quality of life.

§ mMRC (Modified Medical Research Council Dyspnea Scale) scores scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.

** BODE Index score ranges from 0 to 10 based on a multidimensional scoring system to include FEV_1, body-mass index, 6 Minute Walk Distance, and the modified MRC dyspnea score. Higher scores denote a greater risk of mortality.

††: Wilcoxon signed-rank test.

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Table 2: Effectiveness Endpoints for the Intention-to-Treat[a] Population

Outcome	EBV (n=128)	SoC (n=62)	Between Group Difference EBV – SoC (95% CI)	p-value
Primary Endpoint [b]				
Percent of Subjects with Post-BD FEV_1 (L) improvement of ≥15%	47.7%	16.8%	31.0% (18.0%, 43.9%)	<0.001
Secondary Endpoints [c] **(Change from Baseline to 12-months, mean ± SD (n))**				
Post-BD FEV_1				
Volume (L)	0.104 ± 0.200	-0.003 ± 0.194	0.106 (0.047, 0.165)	<0.001
Percent Change (%)	17.16 ± 27.93	-0.80 ± 26.94	17.96 (9.84, 26.09)	<0.001
6MWD (m)	12.98 ± 81.54	-26.33 ± 81.50	39.31 (14.64, 63.98)	0.002[c]
SGRQ score (points)	-7.55 ± 15.71	-0.50 ± 15.50	-7.05 (-11.84, -2.27)	0.004[c]
TLVR				
Volume (L)	-1.142 ± 0.702	NA		
Percent Change (%)	63.8 ± 36.16	NA		
Additional Endpoints (Change from Baseline to 12-months, mean ± SD (n)) [d]				
FEV_1 (% predicted) [e]	4.0 ± 7.84 (128)	-0.3 ± 4.41 (62)	4.2 (2.1, 6.4)	<0.001
RV (L)	-0.49 ± 0.83 (112)	0.03 ± 0.66 (58)	-0.522 (-0.77, -0.27)	<0.001
FRC (L)	-0.412 ± 0.768 (112)	0.014 ± 0.509 (58)	-0.425 (-0.65, -0.20)	<0.001
TLC (L)	-0.319 ± 0.621 (112)	-0.031 ± 0.467 (58)	-0.288 (-0.47, -0.11)	0.002
RV/TLC	-0.045 ± 0.079 (112)	0.005 ± 0.059 (58)	-0.50 (-0.07, -0.03)	<0.001
IC/TLC	0.03 ± 0.07 (112)	-0.004 ± 0.04 (58)	0.03 (0.02, 0.05)	<0.001
DLCO (mL CO/min/mm Hg)	0.559 ± 2.410 (112)	-0.310 ± 1.533 (57)	0.870 (0.18, 1.56)	0.013
DLCO (% predicted)	1.80 ± 8.44 (112)	-1.01 ± 6.39 (57)	2.82 (0.31, 5.33)	0.014
mMRC (points)	-0.5 ± 1.17 (113)	0.3 ± 1.03 (59)	-0.8 (-1.1, -0.4)	<0.001
BODE Index (points)	-0.6 ± 1.76 (112)	0.6 ± 1.51 (58)	-1.2 (-1.8, -0.7)	<0.001

Values are means ± SD. Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard-of-Care; Post-BD, Post bronchodilator; FEV1, Forced Expiratory Volume in 1 second; 6MWD, Six-Minute Walk Distance; SGRQ, St. George's Respiratory Questionnaire; NA, Not applicable; RV, Residual Volume; FRC, Functional Residual Capacity, TLC, Total Lung Capacity; IC, Inspiratory Capacity; DLCO, Diffusing Capacity; BODE Index, multidimensional grading system including body mass index, measure of airflow obstruction, Dyspnea score and exercise capacity; mMRC, modified Medical Research Council Dyspnea Scale); CI, Confidence Interval.

a: The Intention-to-Treat analysis set included all subjects who were randomized. Data for the primary and secondary endpoints were imputed for 13 EBV subjects and 3 SoC subjects.

b. Truncated missing values imputed with multiple imputation (propensity score method). Death prior to 12-month endpoint imputed as failure. P-value from chi-square test.

c: Truncated missing values imputed with multiple imputation (propensity score method). Death prior to 12-month endpoint

imputed no change. Values have been adjusted for multiple imputation. P-values, least squares mean, standard deviations and confidence intervals from an analysis of covariance (ANCOVA) with factor of treatment group and the respective baseline value as a covariate (with values adjusted for multiple imputation).

d: No imputation of missing values. Observed means, standard deviations, and confidence intervals are presented together with the number of subjects included. P-values from an analysis of covariance (ANCOVA) with factor of treatment and the respective baseline value as a covariate.

e: For subjects with missing data at 12-months, FEV_1 % predicted values were derived from the volume (L) values that were imputed for the primary endpoint analysis.

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Table 3: Serious Adverse Events Occurring in at Least 3.0% of Subjects in Either Group

	Treatment Period Day of Procedure/Randomization to 45 Days		Longer-Term Period 45 Days from the Study Procedure/Randomization until 12-month Visit Date	
	EBV (N=128)	SoC (N=62)	EBV (N=122)	SoC (N=62)
Death	4 (3.1%)[a]	0 (0.0%)	1 (0.8%)	1 (1.6%)
Pneumothorax	34 (26.6%)*	0	8 (6.6%)	0
COPD exacerbation	10 (7.8%)	3 (4.8%%)	28 (23.0%)	19 (30.6%)
Pneumonia	1 (0.8%)	0	7 (5.7%)	5 (8.1%)
Respiratory failure	2 (1.6%)	0	1 (0.8%)	2 (3.2%)
Arrhythmia	0	0	1 (0.8%)	2 (3.2%)
Diverticulitis	0	0	1 (0.8%)	2 (3.2%)

Counts reflect number of subjects reporting one or more serious adverse events. Subjects are counted once.
a: Two (2) subjects had DNR orders that prevented further intervention.
*: $p<0.05$, Fisher's Exact test

Table 4: Respiratory Serious Adverse Events Rates – Site Reported and CEC Adjudicated Event Rates

Serious Respiratory Adverse Events	Treatment Period Day of Procedure/Randomization to 45 Days			Longer-Term Period 45 Days from the Study Procedure/Randomization until 12-month Visit Date		
	Serious Adverse Event Rates (Events/45 Days) [a]			Serious Adverse Event Rates (Events//Year) [b]		
	EBV (N=128)	SoC (N=62)	p-value[c]	EBV (N=128)	SoC (N=62)	p-value[c]
Pneumothorax						
Investigator Reported	0.267	0.00	<0.001	0.074	0.00	0.013
CEC Adjudicated	0.275	0.00	<0.001	0.074	0.00	0.013
COPD Exacerbations						
Investigator Reported	0.079	0.047	0.423	0.371	0.573	0.080
CEC Adjudicated	0.110	0.047	0.150	0.352	0.573	0.053
Pneumonia						
Investigator Reported	0.008	0.00	0.369	0.065	0.118	0.287
CEC Adjudicated	0.024	0.00	0.120	0.056	0.118	0.196
Hemoptysis						
Investigator Reported	--	--	--	0.019	0.00	0.215
CEC Adjudicated	--	--	--	0.028	0.00	0129
Respiratory Failure						
Investigator Reported	0.016	0.00	0.204	0.009	0.059	0.078
CEC Adjudicated	0.024	0.00	0.120	0.019	0.099	0.033

a: Adverse Event Rate for the Treatment Period calculated as “Events/45 Days”.
b: Adverse Event Rate for the Longer-Term Period calculated as “Events/Year”.
c: p-value from Poisson regression adjusted for each subject's length of follow-up.

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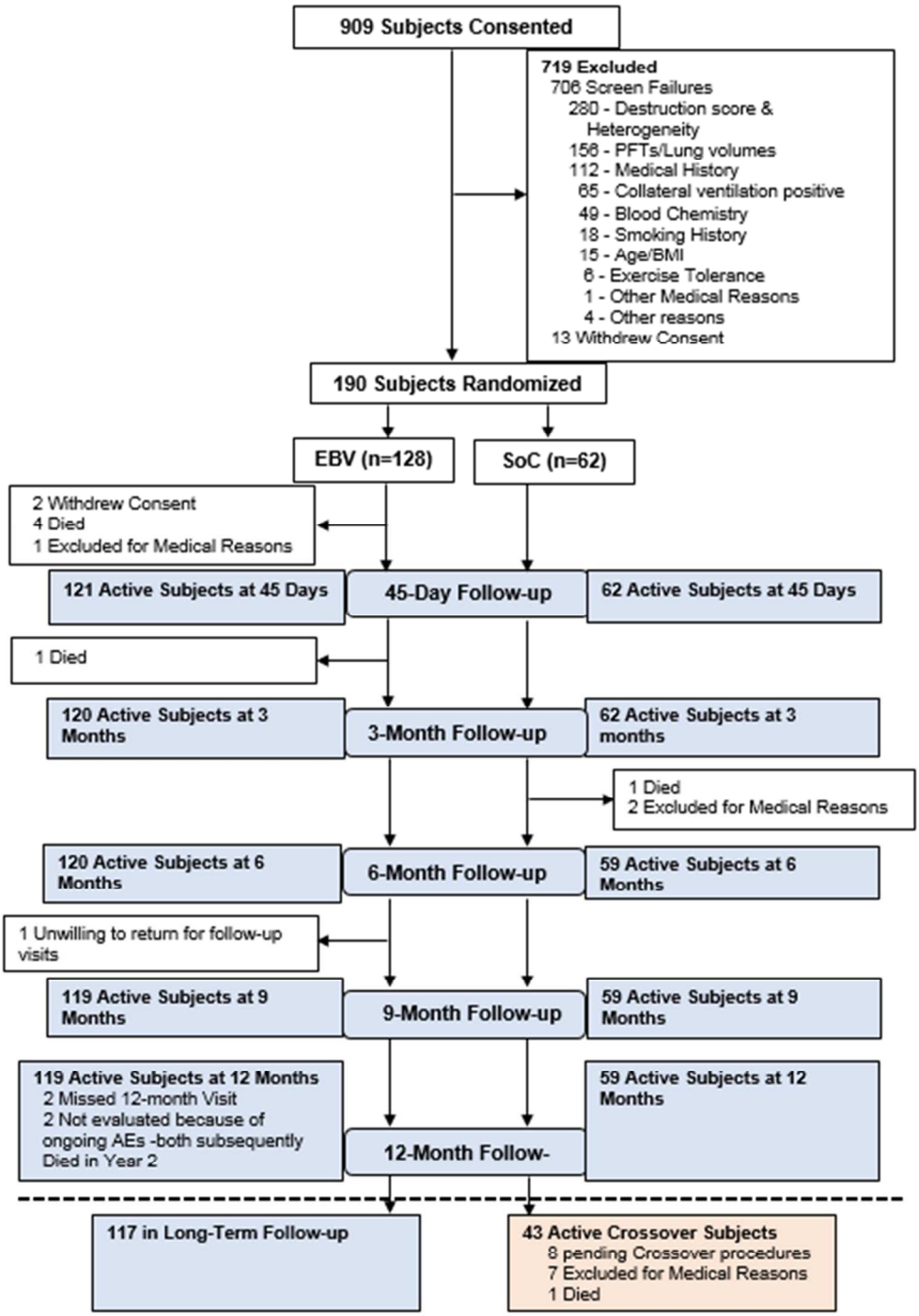

Figure 1: CONSORT Flow Chart

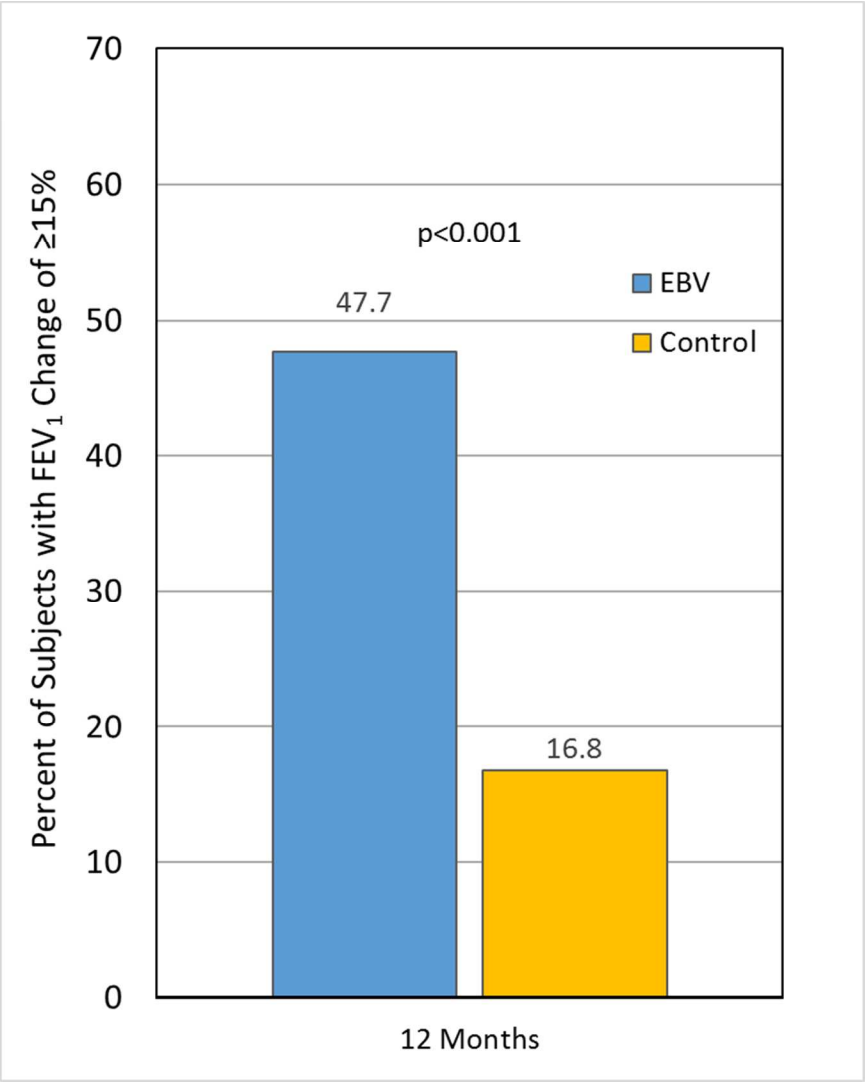

Figure 2: Percent of Subjects with FEV_1 Change from Baseline to 12-months of ≥15%. Bars represent the percent of subjects with an FEV_1 (L) improvement of ≥15% from Baseline to 12-months. (■) EBV group, (■) SoC group. p-value for Chi-square test.

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3a 3b 3c

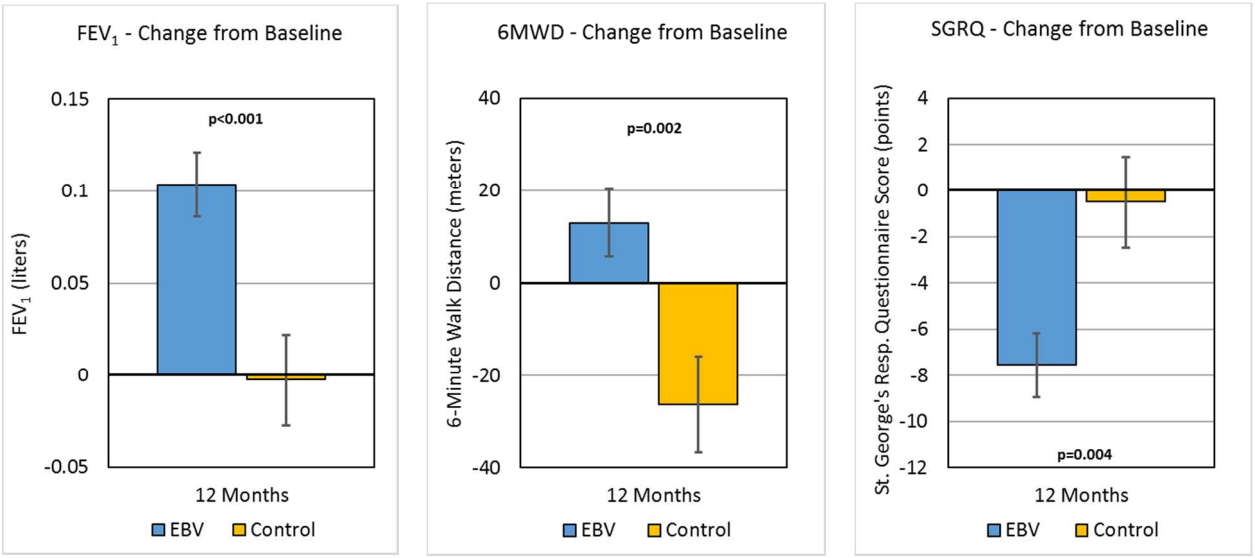
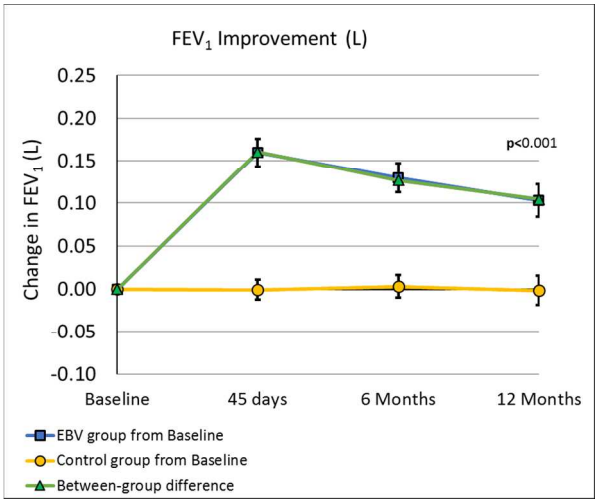


Figure 3: Secondary Endpoints. Changes from Baseline to 12-months for FEV_1 (L, Figure 3a), 6-Minute Walk Distance (m, Figure 3b), and St. George's Respiratory Questionnaire (points, Figure 3c). Values are Least Square Means ± SEM for n=128 (EBV) and n=62 (SoC).

p-values, least squares mean and SEMs from an analysis of covariance (ANCOVA) with factor of treatment and the respective Baseline value as a covariate. Values have been adjusted for multiple imputation. Truncated missing values imputed with multiple imputation (propensity score method). Missing values imputed as baseline carried forward for subjects that died prior to completing 12-month visit. To control the family-wise type I error rate at 5%, the Hochberg step-up procedure was utilized.

4a



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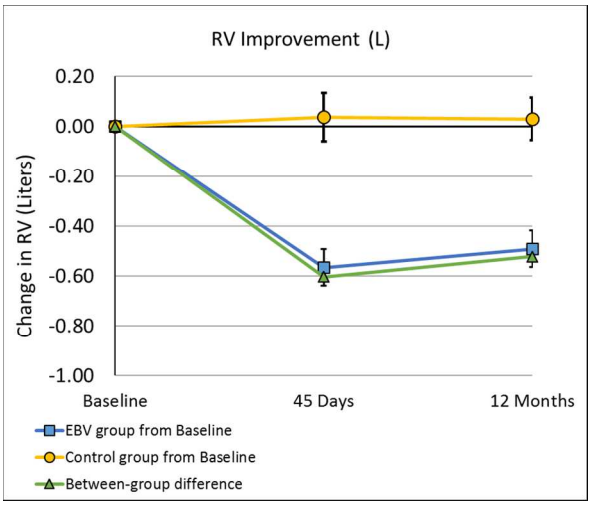

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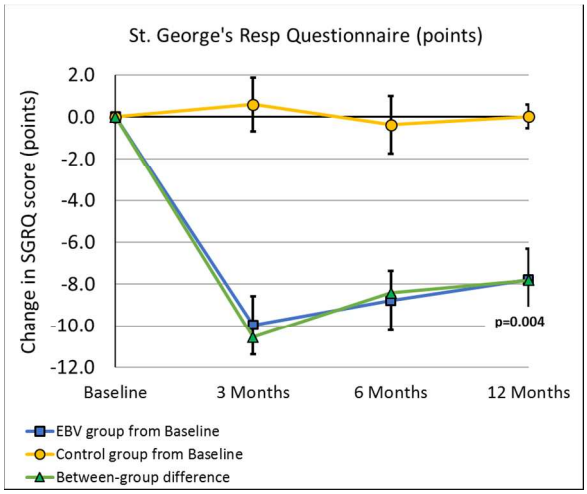

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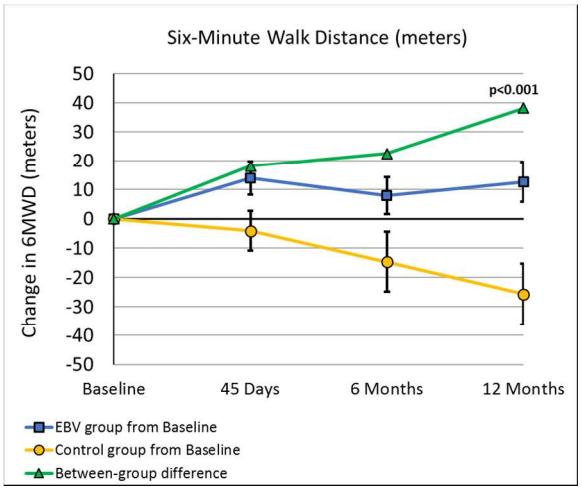

Figure 4: Changes over time from Baseline out to 12-months for Key Outcomes. Data presented are raw means ± SEM for changes from baseline to later time points post-bronchoscopy for EBV ( ), SoC ( ), and difference between EBV and SoC ( ).

Figure 4a: FEV_1 (L); Figure 4b: Residual Volume (L); Figure 4c: St. George's Respiratory Questionnaire; Figure 4d: 6-Minute Walk Distance (m).

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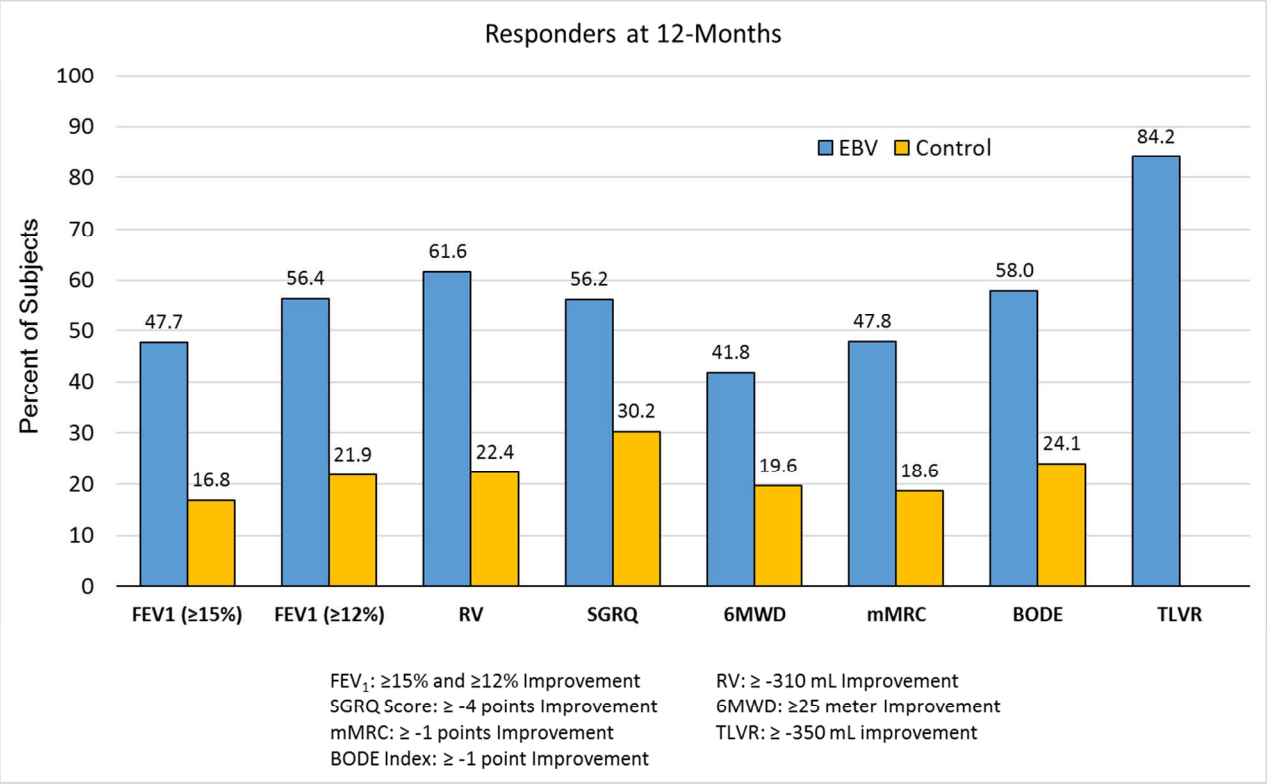
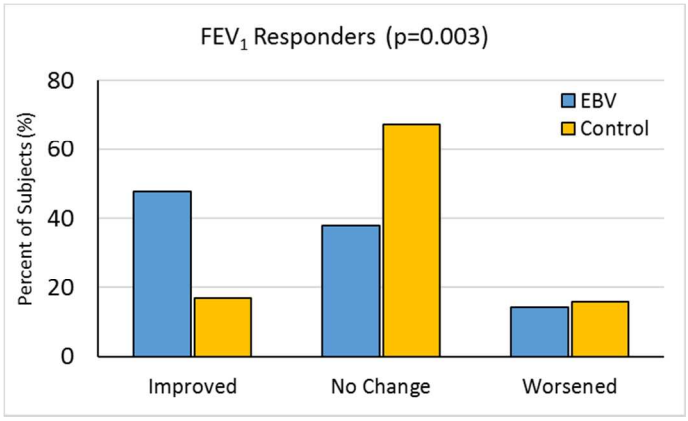


Figure 5: Responders Based on Minimal Clinically Important Difference (MCID) for Assessed Variables

6a



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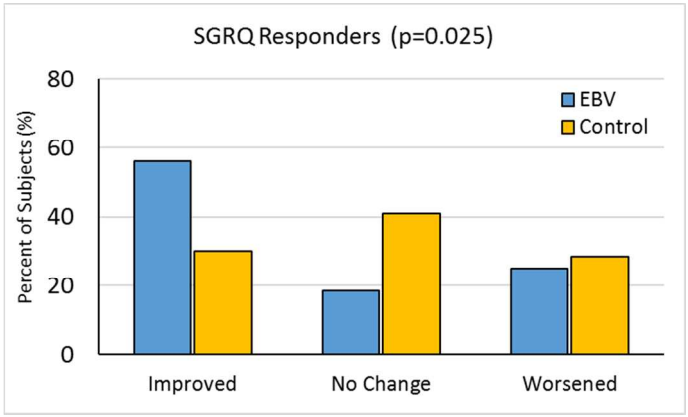

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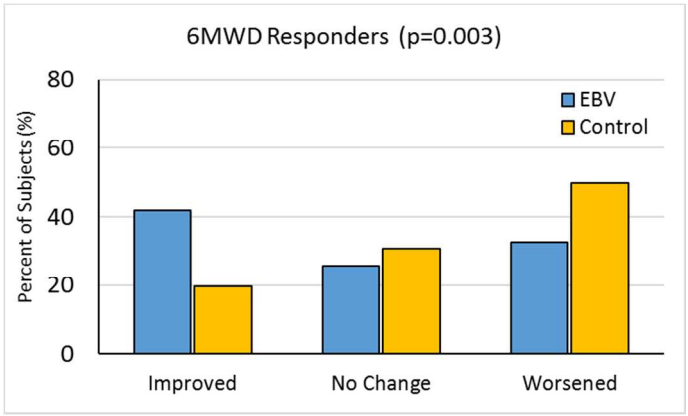

Figure 6: Responders Based on Minimal Clinically Important Difference for FEV_1, SGRQ and 6MWD. Percent of subjects categorized as Improved, no change or worsened based on Minimal Clinically Important Difference (MCID) for each measure. 6a: FEV_1: Improved (≥15% change); No change (<15% to ≤ -15% change); Worsened (< -15% change). 6b: SGRQ: Improved (≤ -4 points change); No change (> -4 to ≤ 4 points change); Worsened (> 4 points change). 6c: 6MWD: Improved (≥26 m change); No change, <26 m to -26 m change); Worsened ≤ - 26m change). Intermittent missing

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values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Death prior to1-year endpoint imputed as Worsened. P-value from Cochran-Mantel Haenszel (CMH) test for row means scores adjusted for multiple imputation using Wilson-Hilferty transformation.

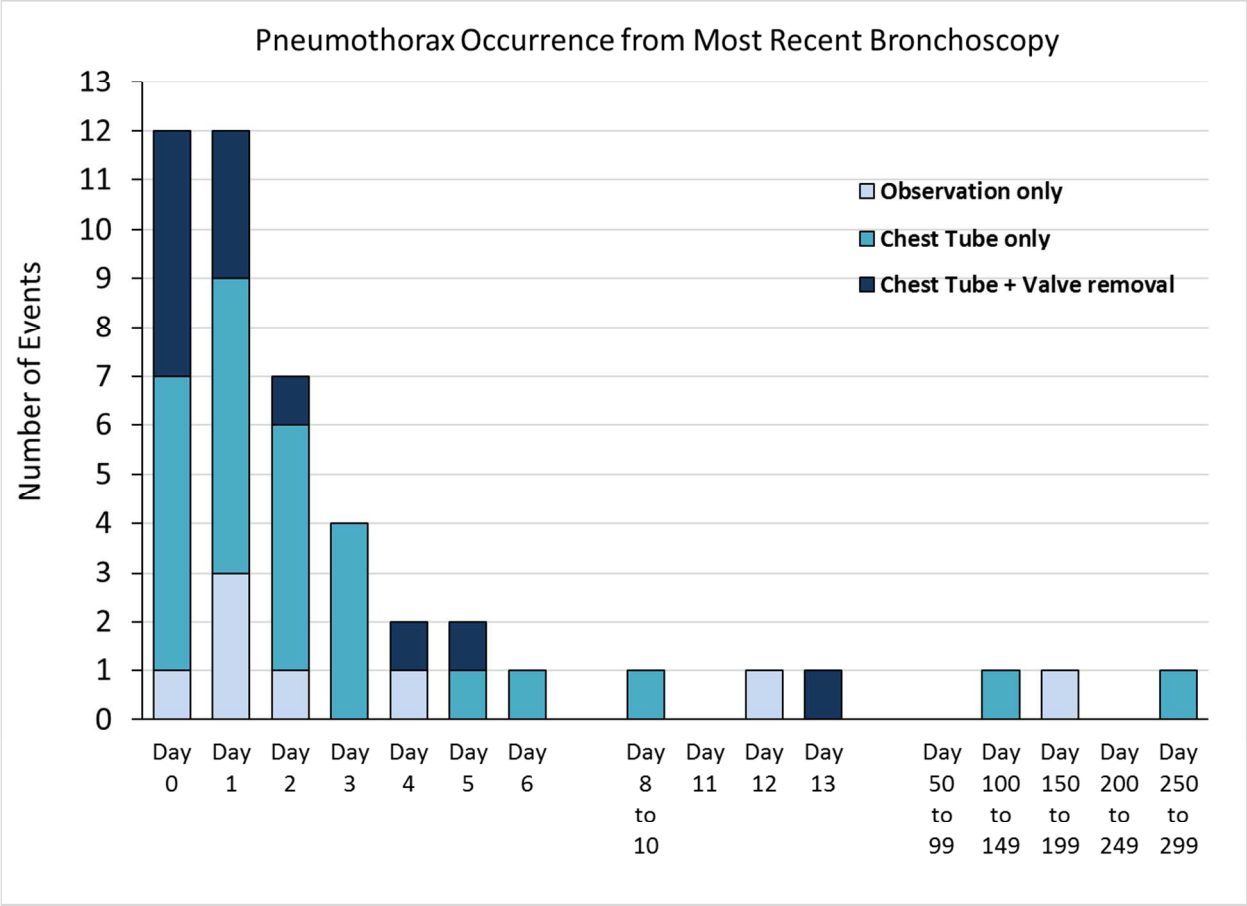

Figure 7: Pneumothorax Occurrence from Most Recent Bronchoscopy. Data represent time of pneumothorax occurrences following most recent bronchoscopy procedure. Each bar represents the number of events per time-period color coded for management of the event: □ Observation only; □ Chest tube only; ■ Chest tube plus Valve removal.

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Online Data Supplement

A Multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

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This supplementary material is provided by the authors to give readers additional information relating to the above-mentioned work.

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Section E1: Inclusion and Exclusion Criteria

The Inclusion/Exclusion criteria involved a 3-phase evaluation process: Screening eligibility, Baseline eligibility, and Procedure eligibility. The required criteria for these 3 phases were:

Screening Inclusion

1. Signed Screening or Study Procedure Informed Consent using a form that was reviewed and approved by the IRB.
2. Age 40 to 75 years.
3. BMI less than 35 kg/m^2.
4. Stable with less than 20mg prednisone (or equivalent) daily.
5. Nonsmoking for 4 months prior to screening interview.

Screening Exclusion

6. Currently enrolled in another clinical trial studying an experimental treatment.
7. Previously enrolled in this study for which protocol required follow up is not complete.
8. Clinically significant (greater than 4 tablespoons per day) sputum production.
9. Two or more COPD exacerbation episodes requiring hospitalization in the last year at screening.
10. Two or more instances of pneumonia episodes in the last year at screening.
11. Unplanned weight loss >10% usual weight <90 days prior to enrollment.
12. History of exercise-related syncope.
13. Myocardial Infarction or congestive heart failure within 6 months of screening.
14. Prior lung transplant, LVRS, bullectomy or lobectomy.
15. Clinically significant bronchiectasis.
16. Unable to safely discontinue anti-coagulants or platelet activity inhibitors for 7 days.
17. Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure >45 mm Hg) or evidence or history of CorPulmonale as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
18. Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan.
19. HRCT collected per CT scanning protocol within the last 3 months of screening date and evaluated by clinical site personnel using 510k cleared CT software shows:
    a. Parenchymal destruction score of greater than 75% in all three right lobes or both left lobes.
    b. Emphysema heterogeneity score less than 15% (Not Applicable for Crossover subjects as of Revision H of protocol).
    c. Large bullae encompassing greater than 30% of either lung.
    d. Insufficient landmarks to evaluate the CT study using the software as it is intended.
20. Left ventricular ejection fraction (LVEF) less than 45% as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
21. Resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT.
22. Dysrhythmia that might pose a risk during exercise or training.
23. Post-bronchodilator FEV_1 less than 15% or greater than 45% of predicted value at screening.
24. TLC less than 100% predicted (determined by body plethysmography) at screening.
25. RV less than 175% predicted (determined by body plethysmography) at screening.
26. DLCO less than 20% predicted value at screening.
27. 6-minute walk distance less than 100 meters or greater than 450 meters at screening.
28. $PaCO_2$ greater than 50mm Hg (Denver greater than 55 mm Hg) on room air at screening.
29. $PaCO_2$ less than 45 mm Hg (Denver less than 30 mm Hg) on room air at screening.

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30. Elevated white cell count (>10,000 cells/μL) at screening.
31. Presence of alpha-1 anti-trypsin deficiency as determined by local laboratory ranges.
32. Plasma cotinine level greater than 13.7 ng/ml (or arterial carboxyhemoglobin >2.5% if using nicotine products) at screening.
33. Any disease or condition that interferes with completion of initial or follow-up assessments.

Consented subjects meeting the Screening criteria had to meet the following Baseline criteria:

Baseline Inclusion

1. Completed a supervised pulmonary rehabilitation program less than equal to 6 months prior to the baseline exam or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred greater than 6 months prior.
2. Baseline evaluation occurred ≤120 days after screening exam.
3. Signed written informed consent to participate in study using a form that was reviewed and approved by the IRB.
4. Continued nonsmoking between initial screening and baseline exams.
5. Willing and able to complete protocol required study follow-up assessments and procedures.
6. FEV_1 between 15% and 45% of predicted value at baseline exam.
7. Post-rehabilitation 6-minute walk distance between 100 meters and 500 meters at baseline exam.
8. Current Pneumococcus vaccination.
9. Current Influenza vaccination.

Baseline Exclusion

10. Myocardial infarction or diagnosis of congestive heart failure between screening and baseline exams.
11. Fever or other clinical evidence of active infection at baseline exam.
12. Two or more COPD exacerbation episodes between screening and baseline exams.
13. Two or more pneumonia episodes between screening and baseline exams.

Subjects who successfully completed the Baseline evaluation signed a Procedure Consent Form (if not previously signed) and underwent a bronchoscopy procedure for evaluation of collateral ventilation and final determination of inclusion in the Study if the following criteria were met:

Procedure Eligibility Inclusion

1. Procedure occurs < 60 days following baseline exam.
2. Continues to meet all screening and baseline eligibility criteria.
3. Little or no collateral ventilation (CV-) as determined using the Chartis System.

Procedure Eligibility Exclusion

1. Evidence of collateral ventilation (CV+) as determined using the Chartis System.
2. Collateral ventilation could not be determined using the Chartis System.
3. Collateral ventilation assessment was not conducted using the Chartis System.

Section E2: Study Design and Methods

Prospective, randomized, controlled, one-way crossover multi-center trial. Planned to enroll 183 subjects with heterogeneous emphysema at a maximum of 30 sites. The final enrollment was 190 subjects.

- Interested patients signed a Screening Informed Consent or a Study Participation Informed Consent and underwent a review of medical history, and completed clinical assessments including a High Resolution Computed Tomography (HRCT) to determine if they met the screening Inclusion/Exclusion criteria.
    - HRCT review at this stage was performed by trained personnel at the Investigational sites. The software used to analyze the HRCT scans was Myrian (510k cleared – K071000 from Intrasense (Montpellier, France). HRCT scans were analyzed to determine the destruction scores of each lobe at -910 Hounsfield units (HU) and selection of "target" lobe(s).
- Subjects meeting the screening Inclusion/Exclusion criteria underwent "Baseline" eligibility screening that included spirometry assessment, and 6MWT. Baseline screening was performed after the subjects had completed a mandated pulmonary rehabilitation program.
    - A study candidate who had completed a supervised pulmonary rehabilitation program within six months prior to the screening visit, or who was regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than six months prior, could proceed to baseline testing provided that the pulmonary rehabilitation program was documented and met the criteria specified in the CIP.
    - A study subject who did not meet the pulmonary rehabilitation program criteria at screening had to initiate attendance to a pulmonary rehabilitation program that included at least two visits to the rehabilitation center per week. Minimum attendance of eight visits was required to fulfill the pulmonary rehabilitation program requirement.
- Eligible subjects who met the Baseline Inclusion/Exclusion criteria signed a Study Participation Informed Consent (if one had not been signed initially) and underwent additional evaluations including a bronchoscopy procedure for assessment of collateral ventilation status using the Chartis® Pulmonary Assessment System. Examples of CV negative and CV positive read-outs from the Chartis system are shown in Figure E1.
- Subjects who met the Procedure eligibility criterion of little or no collateral ventilation between at least one of the target and ipsilateral lobes (CV-) were randomized 2:1 (EBV: Control; SoC) through the EDC portal (iMedNet). The scheme for target lobe determinations is shown in Figure E2.
    - Subjects who had collateral ventilation or indeterminate collateral ventilation between the target and ipsilateral lobes were not eligible for further participation. Subjects were recovered from the bronchoscopy procedure and exited from the study.
    - Subjects randomized to the EBV group underwent EBV placement.
    - Subjects randomized to the Control group were recovered from the bronchoscopy procedure.

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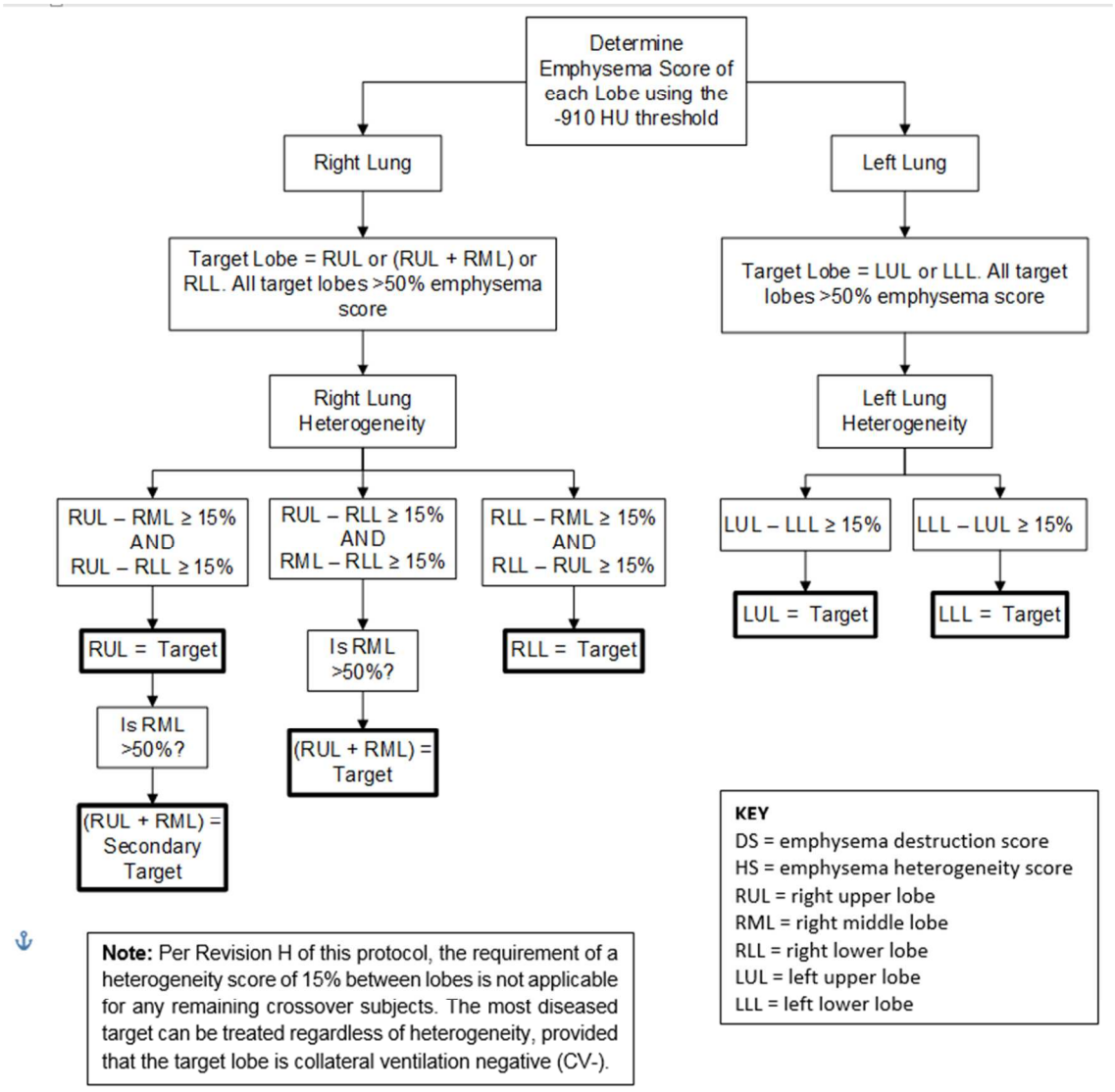
- All subjects maintained a daily diary (hard-copy form) for 7 days prior to the scheduled bronchoscopy procedure and were provided an electronic diary with instructions to complete it daily through the 1-year follow-up visit.
- All subjects were required to complete a protocol specified pulmonary rehabilitation program (20 sessions).
- Subjects randomized to the EBV treatment arm had the Zephyr EBVs placed in the appropriate airways in the target lobe. The EBVs could be placed at the lobar, segmental, or sub-segmental levels, in this order of preference, depending on the lung anatomy of the study subject. The size of the EBVs deployed and the location of each deployment was recorded on the Procedure form. Only one lobe was treated in each study subject unless the target was the combination of the Right Upper Lobe and the Right Middle Lobe (Note: this RUL+RML combination as a target was introduced with Rev F of the Protocol.
- Subjects randomized to the EBV group and who received EBVs were required to stay in the hospital for at least 5 nights. A chest X-ray was taken within an hour (± 30 minutes) of the bronchoscopy procedure. During the hospital stay, chest X-rays were obtained daily on Day 0 (procedure day), Day 1, Day 2, Day 3, Day 4, and Day 5. The Investigational Site was asked to keep a chest tube set by the subject bedside if the subject developed a pneumothorax. If a study subject developed a post-procedural pneumothorax and the hospitalization extended beyond 5 days, additional chest X-rays beyond Day 5 were obtained at the discretion of the study physician, with a protocol mandated chest X-ray on the day of discharge. At discharge, EBV subjects were provided a Medical Alert Card, Treated Study Participant Bracelet, Transferring Instructions if Late Pneumothorax, and Post-Discharge Instructions.
- Both the EBV and Control group subjects continued to receive optimal medical management according to current clinical practice (GOLD 2013 recommendation).

Figure E1: Target Lobe Selection



Notes:

1. Emphysema score refers to the Emphysema Destruction score measured as the percentage of voxels of less than -910 Hounsfield units on CT. Heterogeneity refers to the difference in the Emphysema Destruction scores between lobes.
2. Based on the algorithm above, the treated lobe was not always the most destructed lobe.

- Any subject who received EBV treatment could undergo EBV adjustment, EBV removal, or EBV replacement while participating in the study. In the case of a secondary EBV procedure(s), the follow-up schedule was calculated from the date of the Index procedure (initial treatment date).
    - EBV group subjects had a HRCT performed at 45 days after the procedure to verify technical success of valve placement. To ensure that complete occlusion

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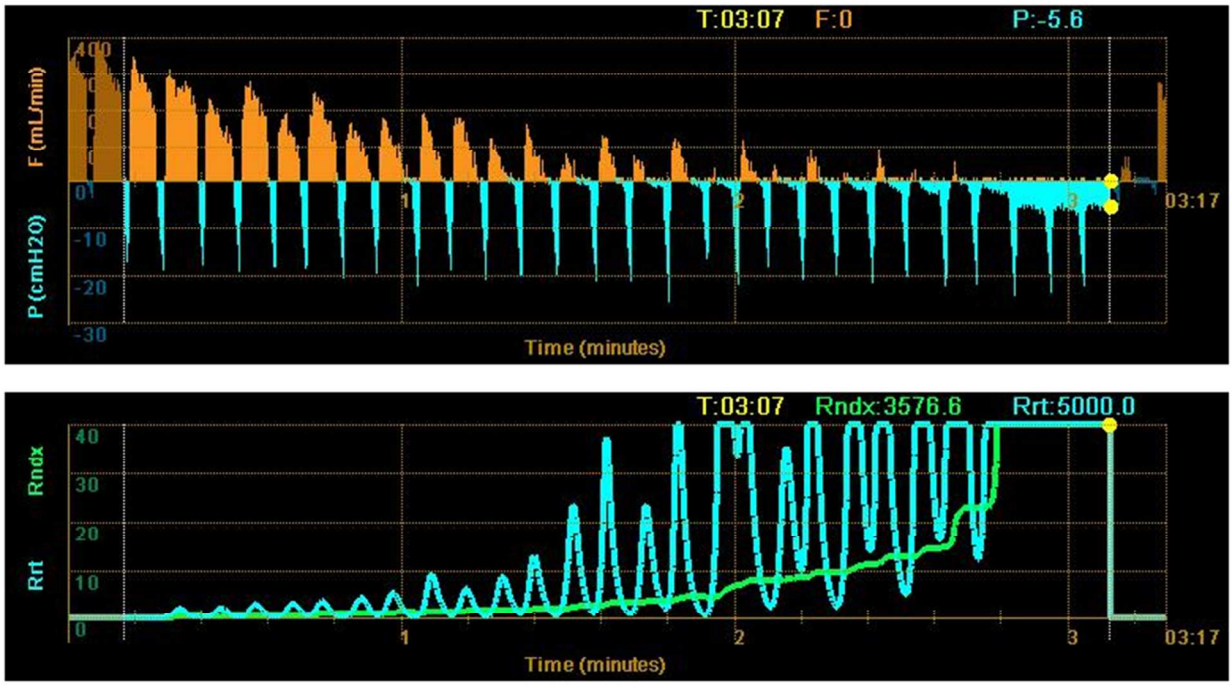
of the treated lobe was achieved, the Investigator had the opportunity to consider an adjustment of the EBV when there was clinical evidence showing that a valve was not adequately placed to block the airway leading into the treated lobe. A one-time adjustment of the EBVs was part of the study procedure since clinical effect with the EBV is thought to be associated with proper placement of the EBVs to achieve lobar occlusion.

- An EBV adjustment procedure could be performed only once for a study subject and within 75 days of the Index procedure. If the subject was experiencing an illness at this time (e.g. COPD exacerbation), the EBV adjustment could be delayed for up 90 days post-procedure. Investigators could consider valve adjustment only if both of the following conditions were met:
  1. The 45-day HRCT scan, as read by the Imaging Core Lab (MedQIA) and measured using FDA cleared software designed to evaluate HRCT changes, showed less than 50% volumetric reduction in the EBV-treated lobe.
  2. The 45-day HRCT scan, as read by the Imaging Core Lab (MedQIA), demonstrated signs indicative of incomplete occlusion, including no valve in a segmental airway, anatomic variation resulting in the valve not occluding accessory branches, leakage around the valve, and incorrect placement.
- Study Investigators could consider removing EBVs due to the occurrence of an adverse event. EBVs could be removed according to the Manufacturer's Instructions for Use.
- Study Investigators could consider replacing valves for study subjects who expectorated a valve(s) or in cases where the valve(s) was removed due to an adverse event after the resolution of the adverse event. Up through the 1-year follow-up time point, EBVs could be replaced up to a maximum of 2 times. The treating physician would determine the timing of a EBV replacement on an individual subject basis.

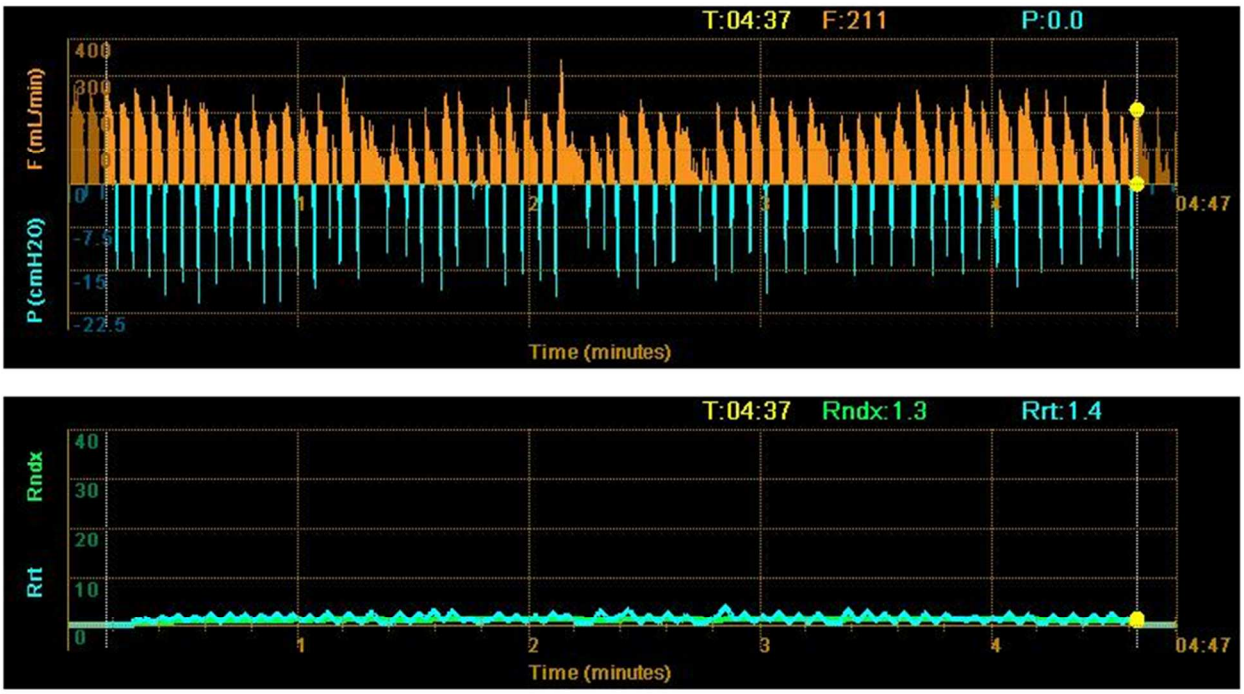
- All study subjects had the following protocol defined visits and underwent specific assessments as identified in the CIP for each visit including, vitals, physical examination, lung function assessments, lung volume measurements, Quality of Life questionnaires, solicitation of adverse events, and collection of Daily Diary records:
  - Daily Follow Up Phone Call for 10 Days after Discharge (up to 11:59 pm) - EBV Treatment Arm Only.
  - Day 7 after Discharge Visit (+ 1 business day) – EBV Treatment Arm Only.
  - Day 30 Visit (± 5 days) - EBV Treatment Arm Only.
  - Day 45 Visit (± 10 days).
  - 3 Month Visit (± 14 days).
  - 6 Month Visit (± 21 days).
  - 9 Month Visit (± 21 days).
  - 1 Year Visit (± 45 days).
  - Annual Visits (± 60 days) out to 5 years only for EBV treated subjects.
- Subjects in the Control group if eligible, were offered to be crossed over to the EBV treatment arm after completing their 12 months follow-up and planned to be followed up for an additional 5 years.
- Adverse events were solicited during each visit and during any unscheduled visit.

Figure E2: Examples of Collateral Ventilation (CV) Negative and CV Positive Assessments from the Chartis® System

CV Negative (CV-) Chartis assessment



CV Positive (CV+) Chartis assessment



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Section E3: Randomization

Study participants who were determined to meet screening, baseline, and procedure eligibility criteria were randomly assigned to Study Treatment (EBV or Control). Random assignment was performed using a stratified permuted block design, generated separately for each clinical site, with assignment stratified by anatomical site of the planned treatment (e.g. right lung or left lung). The randomization schedule was not stratified by the target lobe. Mixed Block sizes of 3 and 6 were used.

Section E4: Special Consideration for Standardization of Critical Assessments

To ensure data visibility and uniformity in the collection of key study data points and patient selection, the Investigational Sites were required to use standardized equipment and software.

1. **Determination of Emphysema Destruction Scores and Heterogeneity for Subject Eligibility:** Standardization of the HRCT reading for target lobe selection was performed using the Myrian software (Intrasense, Montpellier, France) for the HRCT quantitative analysis. All Investigational Sites were provided a laptop with licensed Myrian software for quantification of emphysema destruction score to complete the bronchoscopy plan based on the Myrian report. Training on the software functionalities and specific HRCT segmentation techniques was provided by Pulmonx. All data points were further monitored for accuracy.

2. **Spirometry: To reduce variability in the collection of the Spirometry data, all Investigational Sites utilized** the ERT MasterScope (eReserarch Technology, Philadelphia, PA), a central diagnostic station attached to a Spirometer, to capture the FEV1 and FVC measurements. Training on the on the spirometer equipment, including calibration and standardized techniques, and the associated MasterScope system functionalities was provided by ERT. System access was only granted after a proficiency test was reviewed and approved by an ERT clinical specialist. A data surveillance piece was also embedded in the system and all data captured through the MasterScope went through three levels of control for quality assurance.

3. **Patient Questionnaires:** The electronic diary and three of the patient centric questionnaires (SRGQ, EQ-5D and SF-36) were also integrated with the ERT MasterScope System. The three quality of life questionnaires were completed with a special recording pen and linked to a unique pattern and number to ensure integrity of the data. The Daily Diary was programmed with time windows and audible alerts to ensure regularity in the completion of the questions by the subjects. Training on these components was provided by a certified ERT trainer or qualified Pulmonx Clinical Team member. All data captured through the system was controlled for quality assurance.

Section E5: Sample Size Rationale

The results of two prospective studies were used to inform the sample size estimation. The Endobronchial Valve for Emphysema Palliation Trial ("VENT Pivotal Trial", IDE#G020230, NCT00129584) was a multi-center, prospective, randomized, controlled study conducted at sites in both the United States and Europe to assess the safety and effectiveness of using the Zephyr EBV device for palliating symptoms associated with severe heterogeneous emphysema. Four hundred ninety-two (492) participants were enrolled into the study and randomized to Zephyr EBV Treatment or medical management (control)[1, 2]. The Chartis Pulmonary Assessment System study is a recently completed prospective post-market study that was conducted in Germany, The Netherlands, and Sweden. The primary objective of the study was to quantify the accuracy of the Chartis System when used to identify targeted treatment lobes as having or not having inter-lobar CV in patients with emphysema who were to be treated using endobronchial valves[3]. The results of both the VENT Study and the Chartis System study showed that treatment effect with the endobronchial valve is correlated with lack of inter-lobar CV[4].

Patients in the VENT Study and in the Chartis Study who were considered to have little or no inter-lobar CV contributed the information used for the sample size estimate. Patients who have little or no lobar CV in the targeted treatment lobe are expected to be good responders to endobronchial valve treatment. For the sample size estimate, a 'responder' was a study participant who had >15% improved FEV_1 after EBV treatment.

Based on the results of these studies, the responder rate in the EBV Study Treatment Group is expected to be approximately 35% at 1 year. The responder rate for the control group is not expected to exceed 10% at 1 year. Assuming a two-sided 0.05 alpha level, study power of 90%, and 2:1 allocation random assignment, a sample size of 147 will be adequate to test for superiority. The study sample size will be increased to 183 to allow for 20% lost to follow-up and incomplete data. Each study site will be allowed to enroll a maximum of 25 study participants.

[1] Sciurba F, Ernst A, Herth F, Strange C, Criner G, Marquette C, Kovitz K, Chiacchierini R, Goldin J, McLennan G. A randomized study of endobronchical valves for advanced emphysema. *N Engl J Med* 2010; 363:1233-44.

[2] Herth FJF, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH, Egan JJ, Gasparini S, Agusti C, Holmes-Higgin D, Ernst A, and the International VENT Study Group. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J*, 2012; 39: 1334-1342.

[3] Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (Updated 2010).

[4] Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L, Schmidt B, Slebos DJ. Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. Eur Respir J 2013; 41:302–308.

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Section E6: Statistical Analysis Methods

E6.1: Descriptive Statistics

Means, standard deviations, medians, and confidence intervals were reported for all continuous variables. Dichotomous variables were reported as percentages and the numerator and denominator were reported and defined.

E6.2: Primary Effectiveness Endpoint Analysis

Both an interim and an end of study (12-month evaluation) analysis for the primary effectiveness endpoint were performed. The primary effectiveness endpoint is the difference between the EBV treatment arm and control arm in percentage of study subjects who reach a threshold of ≥15% improved post-bronchodilator FEV_1, collected post-bronchodilator, at 1 year. The post-bronchodilator FEV_1 value was calculated by determining the percentage change for FEV_1 from baseline to 1-year post-procedure using: ((Baseline Post-bronchodilator FEV_1 subtracted from Post-bronchodilator FEV_1 at 1-year follow-up) / (Post-bronchodilator FEV_1 at Baseline)) for individual study participants. The two arms were compared using the standard normal Z-statistic. If at the time of the Interim analysis, $Z>2.571$, then continuing Crossover of Control arm study participants would be strongly justified since the p-value will be <0.01.

The study hypothesis was tested again at the end of the study (12-month evaluation). The Z-statistic was calculated again, and by considering the interim analysis, required a final critical boundary value of 2.004, per the nTerim program. If the trial is not stopped because of the interim analysis, then the final Z-statistic must be greater than or equal to 2.004 to reject the null hypothesis at the final analysis (at the overall 2-sided 5% significance level).

E6.3: Secondary Effectiveness Endpoint Analysis

Analysis techniques used for each of the secondary endpoints are described below. To control the family-wise type I error rate at 5%, the Hochberg[5] step-up procedure was utilized.

a. FEV_1: Difference between study arms in 'absolute change from baseline' for FEV_1 score at 1 year. Descriptive statistics included means, standard deviations and 95% confidence intervals. An analysis of covariance (ANCOVA) with factor of treatment and baseline FEV_1 as a covariate was used to test the difference between treatment arms. P-value was adjusted for multiple imputation.
b. 6-Minute Walk Distance (6MWD): Difference between study arms in 'absolute change from baseline' for 6MWD at 1 year. Descriptive statistics included means, standard deviations and 95% confidence intervals. An analysis of covariance (ANCOVA) with factor of treatment and baseline 6MWD as a covariate was used to test the difference between treatment arms. P-value was adjusted for multiple imputation.
c. St. George's Respiratory Questionnaire (SGRQ): Difference between study arms in 'absolute change from baseline' for SGRQ score at 1 year. Descriptive statistics will include means, standard deviations and 95% confidence intervals. An analysis of covariance (ANCOVA) with factor of treatment and baseline SGRQ as a covariate was used to test the difference between treatment arms. P-value was adjusted for multiple imputation.

[5] Hochberg, Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988; 75(4):800-802

E6. 4: Analysis of Additional Effectiveness Endpoints

Additional effectiveness endpoints measured for both study arms were expected to provide supporting evidence of the effectiveness of EBV treatment. Results are described with summary statistics. These endpoints are described for each study arm separately and comparatively between arms by calculating mean change or difference in proportions, whichever is appropriate for the variable being analyzed.

E6.5: Handling of Missing Data

Every effort was made to collect all data points in the study. Efforts to minimize the amount of missing data included appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating Investigators, monitors, and study coordinators.

- The analysis for the primary endpoint was performed by imputing missing data. Subject death prior to the 1-year visit date is imputed as failure.
- For study subjects with FEV_1 data that are 'intermittent', missing outcomes were imputed by linear interpolation using the FEV_1 value from the latest non-missing data point before the missed data point and the earliest non-missed data point after the missed data point.
- For study subjects with truncated data (e.g. subjects who dropped out or were lost to follow-up), a multiple imputation strategy was performed using the propensity score method. In brief, for a particular outcome, the propensities for study subjects to have missing data (for each treatment group separately), modeled by logistic regression, were grouped into strata based on percentiles of the logistic propensity score model. Within a stratum, a study subject with a missing observation has an imputed value assigned by randomly choosing a value from among the study subjects in the same stratum with non-missing observations. This procedure was repeated 20 times on the entire dataset, resulting in 20 different 'complete' datasets allowing for estimation of the effect on the outcome of interest, accounting for missing data.

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Figure E3: Post-Randomization Follow-up of Study Subjects

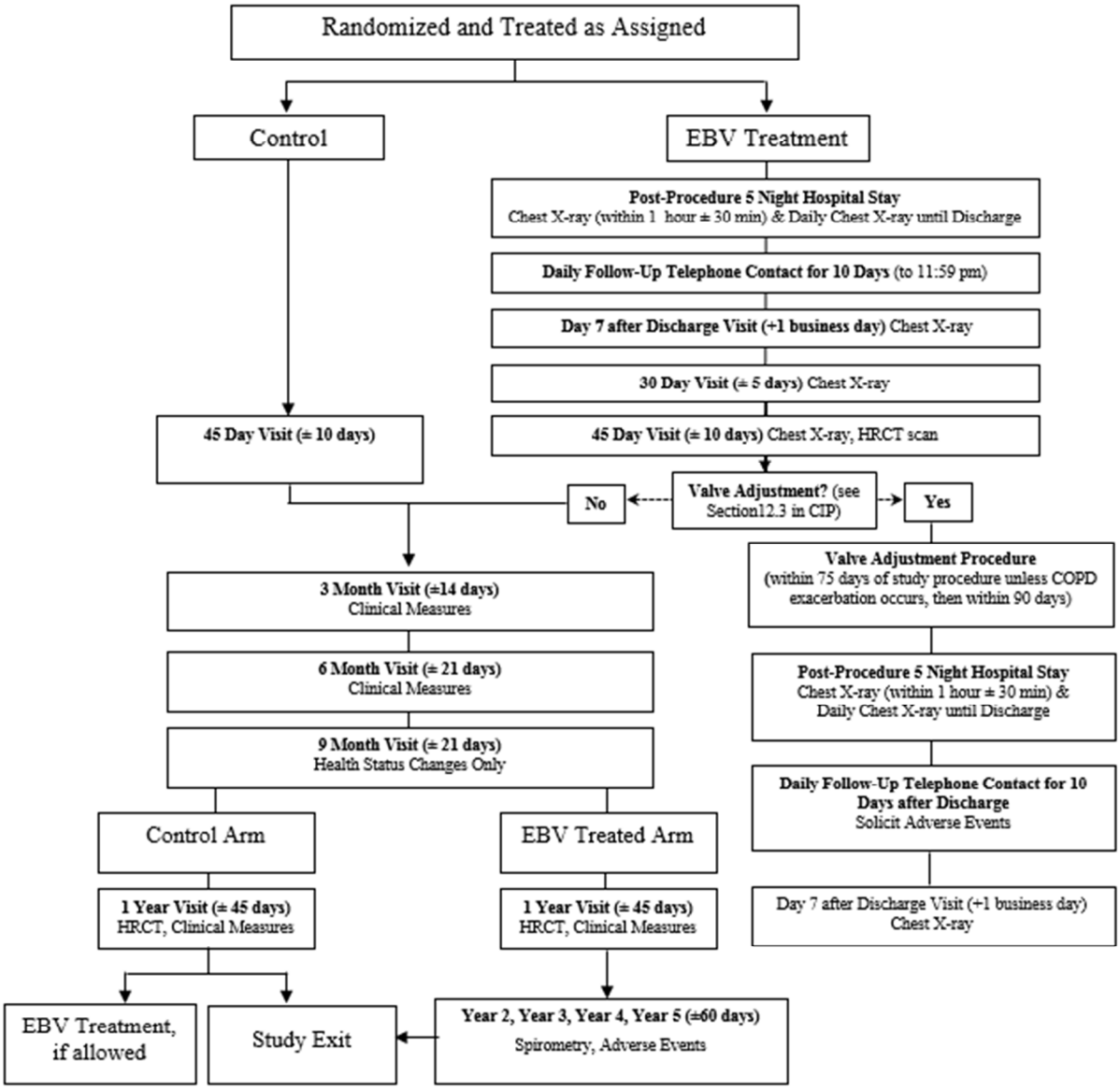

Figure E4: Responders at 6-Months Based on Minimal Clinically Important Difference for Each Outcome Measure (ITT population)

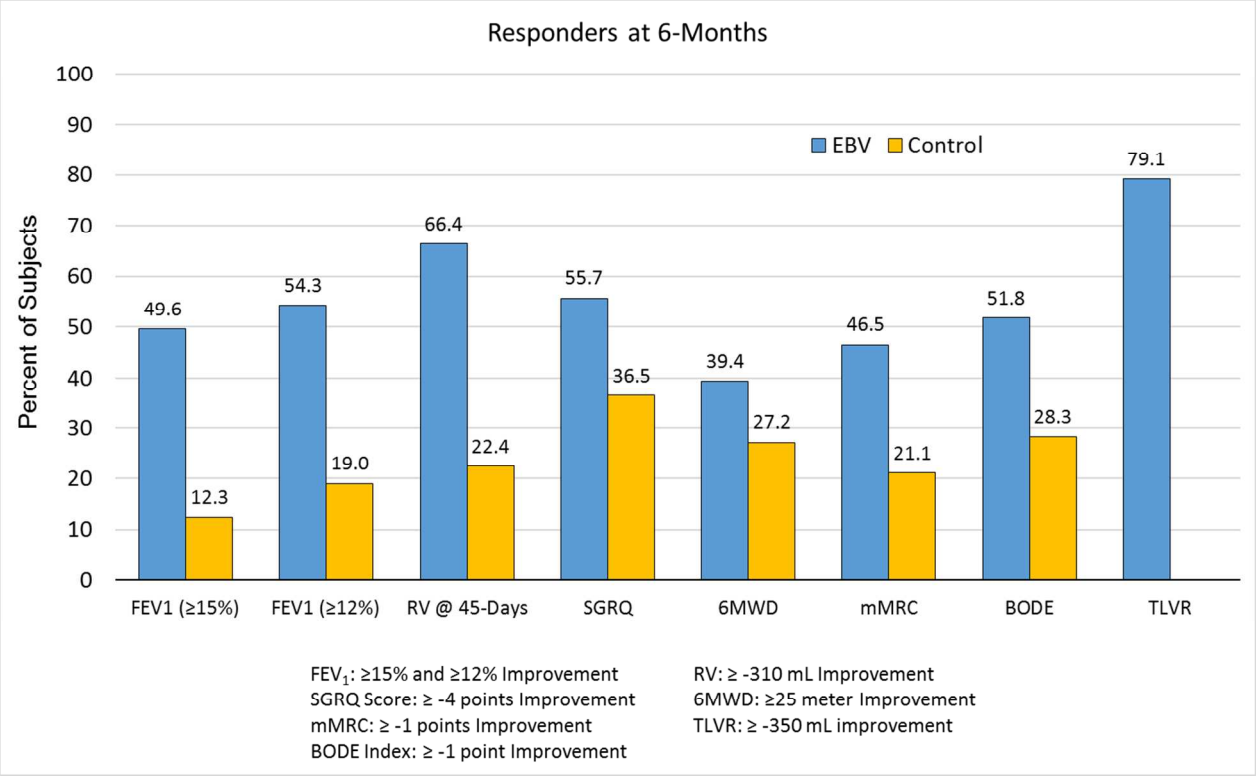

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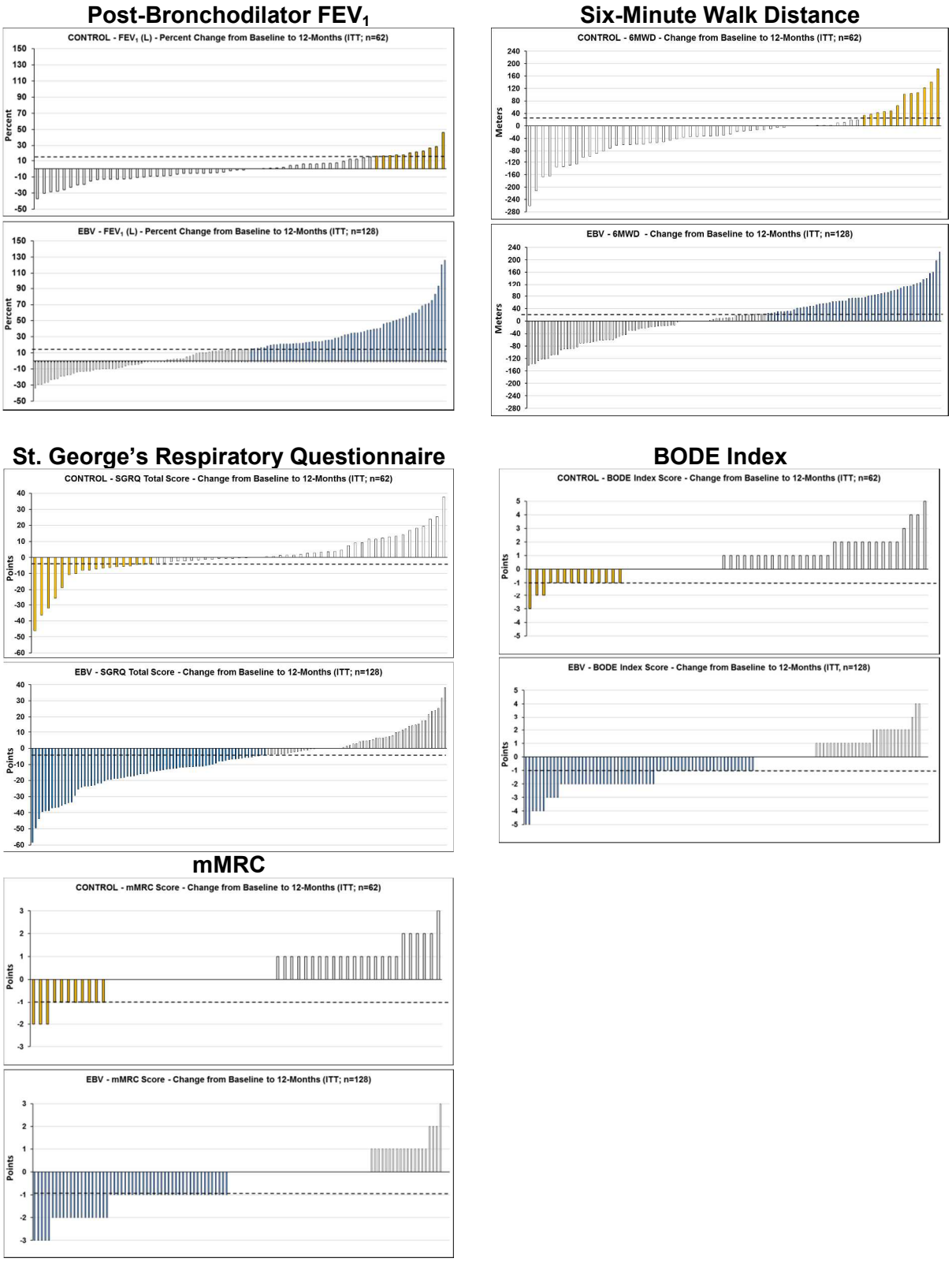
Figure E5: Waterfall Plots with Individual Subject Improvements from Baseline (ITT population)



Legend for Figure E7: Each bar represents an individual subject. Gold (Control) and Blue (EBV) bars represent subjects that met or exceeded minimal clinical important difference (MCID) for FEV_1 of ≥15% improvement in FEV_1 (L); 6MWD (+25 meters); St. George's Respiratory

Questionnaire (- 4 points); BODE Index (-1 point); Modified Medical Research Council Dyspnea Scale (-1 point). Open bars represent subjects who did not meet the MCID. Dotted line represents the MCID.

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Figure E6: Pneumothorax Management Algorithm

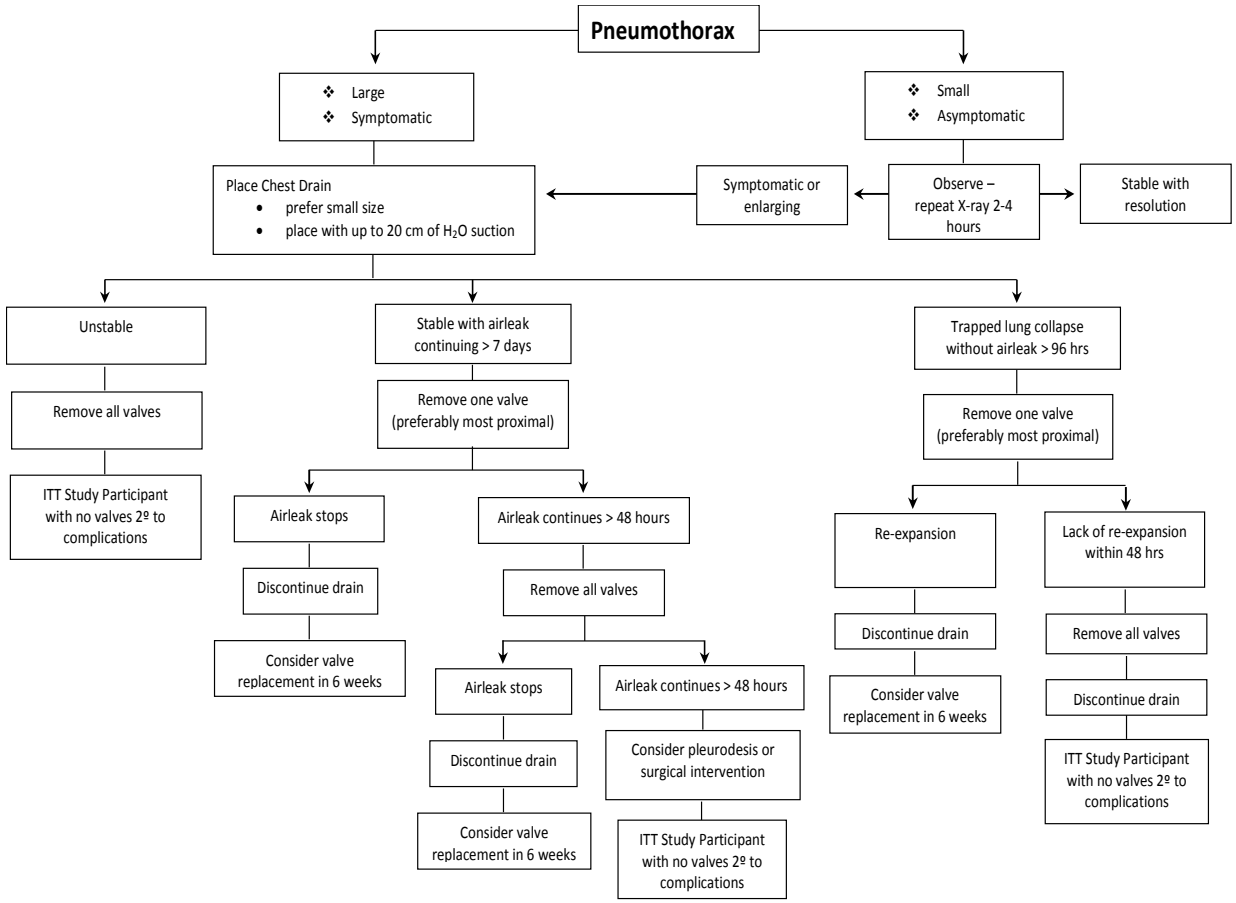

Table E1: Baseline Demographics

Variable	EBV (N=128)		SoC (N=62)		t-test p-value
	Mean	SD (Min, Max)	Mean	SD (Min, Max)	
Age (years)	64.0	6.85 (46 to 75)	62.5	7.12 (45 to 74)	0. 161[a]
Weight (lbs.)	152.41	32.44 (88.0 to 251.33)	153.34	35.09 (85.50 to 230.00)	0.857[a]
Height (inches)	65.69	4.03 (58.0 to 74.0)	66.33	3.44 (60.0 to 73.0)	0.285[a]
BMI (kg/m^2)	24.67	3.90 (15.3 to 36.6)	24.32	4.38 (15.4 to 34.0)	0.577[a]
Pack Year Smoking History	50.78	26.88 (0.0 to 122.5)	48.59	28.48 (2.0 to 135.0)	0.606[a]
Categorical Measures	n (%)		n (%)		
Gender - Males	56 (43.8)		33 (53.2)		0.278[b]
Gender - Females	72 (56.3)		29 (46.8)		
Race					
• American Indian or Alaska Native	1 (0.8)		0 (0.0)		
• Asian	1 (0.8)		0 (0.0)		
• Black or African American	8 (6.3)		3 (4.8)		
• Native Hawaiian or Other Pacific Islander	0 (0.0)		0 (0.0)		
• White	117 (91.4)		57 (91.9)		
• Multiple	1 (0.8)		1 (1.6)		
• Chooses not to provide information	0 (0.0)		1 (1.6)		

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard of Care.
[a] P-value from two-sided t-test assuming equal variance.
[b] P-value from two-sided Fisher's exact test.
Note: Age is calculated from date of informed consent.

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Table E2: Baseline Clinical Characteristics – Lung Function Measures

Variable	EBV (N=128)		SoC (N=62)		t-test p-value
Pulmonary Function Tests and Lung Volumes	Mean (n)	SD (Min, Max)	Mean (n)	SD (Min, Max)	
Forced Expiratory Volume in 1 sec. (FEV_1) – Post-BD (L)	0.763 (128)	0.252 (0.279 to 1.428)	0.752 (62)	0.217 (0.471 to 1.374)	0.767[a]
Forced Expiratory Volume in 1 sec. (FEV_1) – Post-BD (% predicted)	28.0 (128)	7.45 (15 to 45)	26.2 (62)	6.28 (16 to 44)	0.101[a]
Forced Vital Capacity (FVC) (L)	2.596 (128)	0.865 (0.940 to 4.493)	2.631 (62)	0.790 (0.978 to 5.041)	0.792[a]
Forced Vital Capacity (FVC) (% predicted)	71.2 (128)	15.99 (38 to 111)	68.5 (62)	13.59 (37 to 108)	0.248[a]
FEV_1/FVC	0.302 (128)	0.063 (0.17 to 0.46)	0.294 (62)	0.063 (0.19 to 0.50)	0.421[a]
Diffusing Capacity (mL CO/min/mm Hg)	8.528 (126)	3.475 (3.53 to 25.72)	8.342 (61)	2.708 (4.23 to 15.49)	0.741[a]
Diffusing Capacity (% predicted)	34.6 (126)	11.34 (20 to 72)	33.1 (61)	9.84 (20 to 59)	0.393[a]
Residual Volume (RV) (L)	4.709 (126)	1.046 (1.70 to 8.00)	4.759 (61)	0.901 (3.10 to 6.48)	0.752[a]
Residual Volume (% predicted)	224.5 (126)	42.45 (175 to 349)	224.6 (61)	38.86 (175 to 359)	0.987[a]
Total Lung Capacity (TLC) (L)	7.537 (126)	1.593 (5.00 to 13.00)	7.634 (61)	1.369 (5.25 to 10.40)	0.683[a]
Total Lung Capacity (% predicted)	133.5 (126)	21.17 (105 to 307)	130.2 (61)	12.44 (106 to 161)	0.256[a]
RV/TLC	0.631 (126)	0.086 (0.13 to 0.81)	0.626 (61)	0.073 (0.45 to 0.79)	0.689[a]
Functional Residual Capacity (FRC) (L)	5.807 (126)	1.301 (3.73 to 12.18)	5.903 (61)	1.106 (3.80 to 8.10)	
GOLD Stage[c]	54 (42.2%) Stage III 74 (57.8%) Stage IV		16 (25.8%) Stage III 46 (74.2%) Stage IV		0.037[b]

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard of Care; BD, Bronchodilator.
[a] P-value from two-sided t-test assuming equal variance.
[b] P-value from Fisher's Exact test.
[c] Classification of airflow limitation severity in COPD (based post-bronchodilator FEV_1): GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (2017 REPORT)
Note: Baseline results are the latest results prior to EBV or Assessment procedure.
To convert Diffusing Capacity from SI units (mmol / min / kPa) to standard units (mL CO /min /mmHg), values were multiplied by 2.987

Table E3: Baseline Clinical Characteristics – HRCT Characteristics

Variable	EBV (N=128)		SoC (N=62)		t-test p-value
	Mean (n)	SD (Min, Max)	Mean (n)	SD (Min, Max)	
HRCT Characteristics					
Emphysema Destruction score of the Target Lobe at -910 HU*	70.9 (128)	8.52 (50 to 88)	70.9 (62)	8.77 (51 to 86)	0.998[a]
Ipsilateral Lobe Destruction Score (%)	45.4 (128)	11.12 (11 to 68)	44.8 (62)	12.36 (11 to 69)	0.739[a]
Heterogeneity Index †	25.5 (128)	9.85 (15 to 70)	26.1 (62)	9.81 (15 to 61)	0.694[a]

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard of Care; HU, Hounsfield Unit.
[a] P-value from two-sided t-test assuming equal variance.
* Emphysema destruction score was assessed as the percentage of voxels of less than -910 Hounsfield units on CT.
† Volume weighted Heterogeneity Index assessed as the difference in the Emphysema destruction score between the target and the ipsilateral lobe. A difference of ≥15% was required between target and ipsilateral lobes.

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Table E4: Baseline Clinical Characteristics – Blood Chemistry

Variable	EBV (N=128)		SoC (N=62)		t-test p-value
Blood Tests	Mean (n)	SD (Min, Max)	Mean (n)	SD (Min, Max)	
Arterial O_2 Saturation %)	93.2 (127)	2.99 (81 to 99)	93.2 (62)	2.59 (86 to 98)	0.988[a]
PaO_2 (mm Hg)	68.7 (128)	11.62 (45 to 108)	67.8 (62)	11.72 (47 to 127)	0.605[a]
$PaCO_2$ (mm Hg)	40.1 (128)	4.91 (30 to 53)	41.3 (62)	5.33 (27 to 54)	0.118[a]
pH	7.42 (128)	0.032 (7.34 to 7.52)	7.41 (62)	0.031 (7.30 to 7.50)	0.095[a]
Bicarbonate (mEq/L)	26.15 (128)	3.111 (19.2 to 36.0)	26.27 (62)	3.379 (19.2 to 36.2)	0.808[a]
Hemoglobin (g/dL)	14.0 (128)	1.50 (8.3 to 17.2)	14.0 (62)	1.57 (9.8 to 17.2)	0.879[a]
Hematocrit (%)	42.68 (128)	3.932 (32.0 to 51.2)	42.80 (62)	4.502 (28.9 to 51.0)	0.844[a]
Red Blood Cells (10^6/uL)	4.643 (128)	0.503 (3.01 to6.01)	4.651 (62)	0.571 (3.09 To 5.73)	0.921[a]
White Blood Cells (10^3/uL)	7.83 (128)	1.702 (4.1 to 13.7)	7.92 (62)	1.758 (3.4 to 10.7)	0.744[a]
Platelet Count (10^6/uL)	0.264 (128)	0.061 (0.138 to 0.425)	0.266 (62)	0.068 (0.124 to 0.463)	0.887[a]
Serum Fibrinogen (mg/dL)	377.7 (128)	84.86 (186 to 708)	372.6 (62)	82.95 (156 to 547)	0.696[a]

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard of Care.
[a] P-value from two-sided t-test assuming equal variance.
Note: Baseline results are the latest results prior to EBV or Assessment procedure.

Table E5: Baseline Clinical Characteristics – Exercise Tolerance and Quality of Life Measures

Variable	EBV (N=128)		SoC (N=62)		t-test p-value
Exercise Tolerance and Quality of Life Measures	Mean (n)	SD (Min, Max)	Mean (n)	SD (Min, Max)	
6 Minute Walk Distance (m)	311.33 (128)	81.33 (142 to 482)	301.91 (62)	78.54 (102 to 474)	0.450[a]
BORG before 6MWT	1.16 (128)	1.391 (0.0 to 7.0)	1.07 (62)	1.201 (0.0 to 4.0)	
BORG after 6MWT	4.45 (128)	2.174 (0.0 to 10.0)	4.94 (62)	2.282 (0.5 to 10.0)	
SGRQ Total score ‡	55.15 (127)	14.09 (30.1 to 88.1)	53.10 (61)	14.14 (25.9 to 91.8)	0.352[a]
mMRC Dyspnea Grade score §	2.4 (126)	0.97 (0 to 4)	2.2 (62)	0.83 (0 to 4)	0.091[b]
BODE Index **	5.34 (126)	1.52 (2.0 to 10.0)	5.32 (62)	1.56 (2.0 to 9.0)	0.819[b]
CAT Total score ‖	19.2 (128)	6.32 (5 to 37)	19.3 (62)	6.35 (6 to 34)	
EQ-5D Index	0.7 (127)	0.16 (0 to 1)	0.7 (61)	0.16 (0 to 1)	0.647[b]
EQ-5D VAS score	58.4 (121)	20.46 (4 to 100)	53.1 (59)	20.76 (5 to 80)	0.159[b]

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard of Care.

[a] P-value from two-sided t-test assuming equal variance.

[b] P-value from Wilcoxon Rank Sum Test.

Note: Baseline results are the latest results prior to EBV or Assessment procedure.

‡ St. George's Respiratory Questionnaire (SGRQ) scores range from 0 to 100, with higher scores indicating worse quality of life.

§ Modified Medical Research Council (mMRC) Dyspnea Scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.

‖ COPD Assessment Test (CAT) score ranges from 0-40 with higher scores indicating a more severe impact of COPD on a patient's life.

** BODE Index score ranges from 0 to 10 based on a multidimensional scoring system to include FEV_1, Body-Mass Index, 6-Minute Walk Distance, and the modified MRC Dyspnea score. Higher scores denote a greater risk of mortality.

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Table E6: Procedural Details: Lobes Treated and Duration of Chartis Assessment and EBV Placement Procedure

	EBV (N=128)	SoC (N=62)
Duration of Bronchoscopy Assessment (Chartis)[a] (minutes)		
N	1	62
Mean	19	19.5
SD	16.5	13.58
Median	12	18.0
Min. to Max.	2 to 9	2 to 59
Duration of Study Treatment Procedure (minutes)[b]		
N	1	
Mean	34	NA
SD	24.2	
Median	28	
Min. to Max.	4 to 1	
Anesthesia Type		
General Anesthesia	83 (64.8	NA
Conscious Sedation	45 (35.2%)	NA
Treated Lobe		
Left Lower Lobe	15 (11.7	NA
Left Upper Lobe	85 (66.4%)	NA
Right Lower Lobe	6 (4.7	NA
Right Upper Lobe	14 10.9%)	NA
Right Upper Lobe + Right Middle Lobe	8 (6.3%)	NA

a: Refers to the time for the Chartis assessment to determine collateral ventilation.
b: Refers to the procedure time for placement al Zephyr EBVs in the target lobe.

Note: Two subjects (005-008, 013-011) had the procedure completed over 2 days. These subjects are not included in summary of procedure duration.

Table E7: Listing of Subjects Qualified for Adjustment per Day 45 HRCT Results

Subject ID	Randomization Date	Index Bronchoscopy Date	Lobar Occlusion?	Day 45 CT Treated Lobe Volume Reduction (%)	Adjustment Completed?
004-034	21-Apr-2015	21-Apr-2015	No	25	Yes
004-045	22-Jul-2015	22-Jul-2015	No	64	Yes*
004-062	16-Feb-2016	16-Feb-2016	No	20	Yes
013-057	6-Jan-2016	6-Jan-2016	No	34	Yes
014-049	30-Sep-2016	30-Sep-2016	No	26	Yes
015-009	30-Mar-2015	30-Mar-2015	No	28	Yes
015-010	14-Aug-2015	14-Aug-2015	No	12	Yes
022-020	6-May-2016	6-May-2016	No	-1	Yes
030-024	15-Sep-2015	15-Sep-2015	No	30	Yes
031-016	19-Aug-2016	19-Aug-2016	No	-1	Yes
034-029	24-May-2016	24-May-2016	No	3	Yes
004-051	10-Nov-2015	10-Nov-2015	Yes	8	No*
005-008	18-Jun-2014	18-Jun-2014	No	44	No*
006-009	22-Sep-2015	22-Sep-2015	No	10	No*
007-007	31-Mar-2015	31-Mar-2015	No	48	No*
013-011	8-Oct-2014	8-Oct-2014	No	13	No*
013-059	3-Aug-2016	3-Aug-2016	No	16	No*
035-007	28-Jun-2016	28-Jun-2016	No	4	No*

* Subject 004-045: Although the TLVR > 50%, adjustment performed for incorrectly placed valve.
Subject 004-051: Core Lab recommended adjustment, but further analysis of HRCT indicated that the valves were in appropriate location and achieved lobar occlusion. However, subject had and incomplete fissure that could be the cause for incomplete collapse and low TLVR (8%).
Subject 005-008: Core Lab identified incorrectly placed valve located in position b3a. Adjustment not done.
Subject 006-009: Subject refused replacement of valve removed due to Pneumothorax.
Subject 007-007: Adjustment attempted but not successful due to collapsed lobe.
Subject 013-011: Core Lab identified a leak in the valve located in position b1 + 2a. Adjustment not done.
Subject 013-059: Subject was last seen on at the 45-day study visit. The Site learnt of subsequent hospitalization and death of subject.
Subject 035-007: 45-day HRCT sent to Site 7-months late.

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Table E8: Analysis of Oxygen Use Changes from Baseline to 12-Months (Intent-to-Treat Population)

	EBV (N=128)	SoC (N=62)	p-Value
Oxygen Use at 12-Months (N)	115	58	
Less Use	18 (15.7%)	4 (6.9%)	0.019
Same Use	84 (73.0%)	41 (70.7%)	
More Use	13 (11.3%)	13 (22.4%)	

p-value from Cochran-Mantel-Haenszel (CMH) test for row mean scores.

Subjects' oxygen usage varied from no oxygen use to continuous oxygen use. Subjects using oxygen partially or continuously during the day also may have different flow rates depending on activities, rest, and nighttime sleep periods. The varied use of oxygen limits the ability to create aggregate group summaries of flow rate data for comparison.

Table E9: Effectiveness Outcomes at 12-Months for EBV Subjects with All Valves Removed versus EBV Subjects with Valves

Outcome	EBV with All Valves Removed (n=8)	EBV with Valves (n=120)
Primary Endpoint		
Percent of Subjects with Post-BD FEV_1 (L) improvement of ≥15%	15.0%	49.9%
Secondary Endpoints (Change from Baseline to 12-months)		
Post-BD FEV_1		
Volume (L)	-0.114 ± 0.279	0.118 ± 0.204
Percent Change (%)	-7.97 ± 28.95	18.72 ± 30.22
6MWD (m)	-27.9 ± 92.3	15.3 ± 76.1
SGRQ score (points)	2.86 ± 19.34	-8.52 ± 16.49

Values are means ± SD.

Abbreviations: EBV, Zephyr Endobronchial Valve; Post-BD, Post bronchodilator; FEV_1, Forced Expiratory Volume in 1 second; 6MWD, Six-Minute Walk Distance; SGRQ, St. George's Respiratory Questionnaire.

Change calculated as follow-up - baseline. Intermittent missing values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Missing values imputed as baseline carried forward for subjects that died prior to completing 1-year visit.

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Table E10: Adverse Events Occurring within 45 Days in at Least 3% of Subjects in Either Group - Anesthesia Type (Safety Subjects)

	EBV with Conscious Sedation (N=45)		EBV with General Anesthesia (N=83)	
MeDRA Preferred Term	N (%)	95% CI	N (%)	95% CI
Chest pain	18 (40.0%)	(25.7%, 55.7%)	15 (18.1%)	(10.5%, 28.0%)
Pneumothorax	11 (24.4%)	(12.9%, 39.5%)	27 (32.5%)	(22.6%, 43.7%)
COPD exacerbations	10 (22.2%)	(11.2%, 37.1%)	15 (18.1%)	(10.5%, 28.0%)
Cough	7 (15.6%)	(6.5%, 29.5%)	16 (19.3%)	(11.4%, 29.4%)
Pleural effusion	7 (15.6%)	(6.5%, 29.5%)	2 (2.4%)	(0.3%, 8.4%)
Dyspnea	6 (13.3%)	(5.1%, 26.8%)	15 (18.1%)	(10.5%, 28.0%)
Constipation	5 (11.1%)	(3.7%, 24.1%)	3 (3.6%)	(0.8%, 10.2%)
Nausea	5 (11.1%)	(3.7%, 24.1%)	5 (6.0%)	(2.0%, 13.5%)
Hemoptysis	4 (8.9%)	(2.5%, 21.2%)	7 (8.4%)	(3.5%, 16.6%)
Headache	4 (8.9%)	(2.5%, 21.2%)	6 (7.2%)	(2.7%, 15.1%)
Pyrexia	4 (8.9%)	(2.5%, 21.2%)	0 (0.0%)	
Arrhythmia	3 (6.7%)	(1.4%, 18.3%)	2 (2.4%)	(0.3%, 8.4%)
Pneumonia	3 (6.7%)	(1.4%, 18.3%)	3 (3.6%)	(0.8%, 10.2%)
Dizziness	2 (4.4%)	(0.5%, 15.1%)	2 (2.4%)	(0.3%, 8.4%)
Fall	2 (4.4%)	(0.5%, 15.1%)	0 (0.0%)	
Fatigue	2 (4.4%)	(0.5%, 15.1%)	1 (1.2%)	(0.0%, 6.5%)
Hypoxia	2 (4.4%)	(0.5%, 15.1%)	5 (6.0%)	(2.0%, 13.5%)
Wheezing	2 (4.4%)	(0.5%, 15.1%)	1 (1.2%)	(0.0%, 6.5%)
Chest discomfort	1 (2.2%)	(0.1%, 11.8%)	7 (8.4%)	(3.5%, 16.6%)
Functional gastrointestinal disorder	1 (2.2%)	(0.1%, 11.8%)	5 (6.0%)	(2.0%, 13.5%)
Oropharyngeal pain	1 (2.2%)	(0.1%, 11.8%)	9 (10.8%)	(5.1%, 19.6%)
Lower respiratory tract congestion	0 (0.0%)		3 (3.6%)	(0.8%, 10.2%)
Sputum increased	0 (0.0%)		4 (4.8%)	(1.3%, 11.9%)

Abbreviations: EBV, Zephyr Endobronchial Valve.

Counts reflect number of subjects reporting one or more adverse events that map to MedDRA (version 19.0). Subjects are counted once within Preferred Term.

Adverse event with onset date within 45 days of EBV procedure/bronchoscopy assessment.

Table E11: Effectiveness Outcomes at 12-Months for EBV Subjects with Upper Lobe and Lower Lobe Treatments

Outcome	EBV Treated Upper Lobe (n=107)	EBV Treated Lower Lobe (n=21)
Primary Endpoint		
Percent of Subjects with Post-BD FEV_1 (L) improvement of ≥15%	45.9%	57.1%
Secondary Endpoints (Change from Baseline to 12-months)		
Post-BD FEV_1		
Volume (L)	0.096 ± 0.223	0.138 ± 0.182
Percent Change (%)	16.11 ± 31.86	21.87 ± 25.09
6MWD (m)	12.7 ± 77.7	12.1 ± 80.7
SGRQ score (points)	-8.01 ± 17.70	-6.67 ± 11.83

Values are means ± SD.

Abbreviations: EBV, Zephyr Endobronchial Valve; Post-BD, Post bronchodilator; FEV_1, Forced Expiratory Volume in 1 second; 6MWD, Six-Minute Walk Distance; SGRQ, St. George's Respiratory Questionnaire.

Change calculated as follow-up - baseline. Intermittent missing values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Missing values imputed as baseline carried forward for subjects that died prior to completing 1-year visit.

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Table E12: Analysis of Adverse Events Occurring in at Least 3.0% of Subjects in Either Group (Safety Subjects)

	Treatment Period (Day of Procedure/Randomization to 45 Days)		Longer-Term Period (45 Days from the Study Procedure/Randomization until 12-Month Visit Date	
	EBV (N=128)	SoC (N=62)	EBV (N=122)	SoC (N=62)
RESPIRATORY				
Pneumothorax	38 (29.7%)*	0 (0.0%)	8 (6.6%)	0 (0.0%)
Chest pain	33 (25.8%)*	1 (1.6%)	8 (6.6%)	0 (0.0%)
COPD	25 (19.5%)	7 (11.3%)	69 (56.6%)	35 (56.5%)
Cough	23 (18.0%)*	3 (4.8%)	6 (4.9%)	2 (3.2%)
Dyspnea	21 (16.4%)*	2 (3.2%)	16 (13.1%)*	1 (1.6%)
Haemoptysis	11 (8.6%)	1 (1.6%)	12 (9.8%)*	0 (0.0%)
Oropharyngeal Pain	10 (7.8%)	3 (4.8%)	0 (0.0%)	0 (0.0%)
Pleural Effusion	9 (7.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest discomfort	8 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoxia	7 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonia	6 (4.7%)	0 (0.0%)	11 (9.0%)	6 (9.7%)
Sputum increased	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary mass	0 (0.0%)	0 (0.0%)	7 (5.7%)	3 (4.8%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	7 (5.7%)	0 (0.0%)
Bronchitis	0 (0.0%)	0 (0.0%)	6 (4.9%)	3 (4.8%)
Lower respiratory tract congestion	0 (0.0%)	0 (0.0%)	5 (4.1%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	3 (2.5%)	3 (4.8%)
Respiratory failure	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)
NON-RESPIRATORY				
Headache	10 (7.8%)	1 (1.6%)	4 (3.3%)	0 (0.0%)
Nausea	10 (7.8%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation	8 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Functional Gastrointestinal disorder	6 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arrhythmia	5 (3.9%)	0 (0.0%)	2 (1.6%)	2 (3.2%)
Dizziness	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	4 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Infection	0 (0.0%)	0 (0.0%)	10 (8.2%)	4 (6.5%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	2 (1.6%)	4 (6.5%)
Diverticulitis	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard-of-Care
*: $p<0.05$

Table E13: Respiratory Serious Adverse Events of Special Interest Through One Year Visit – Days from Most Recent Bronchoscopy (Safety Subjects)

MedDRA Preferred Term	EBV (N=128)		SoC (N=62)	
	≤45 Days	>45 Days to 1 Year Visit	≤45 Days	>45 Days to 1 Year Visit
COPD Exacerbation	13	37	3	29
Dyspnea	4	3	0	0
Hemoptysis	0	2	0	0
Pleural effusion	2	1	0	0
Pneumonia	1	7	0	6
Pneumonia Distal to Valve Implant	0	1	NA	NA
Pneumothorax	39	3	0	0
Respiratory failure	2	1	0	3

Abbreviations: EBV, Zephyr Endobronchial Valve; SoC, Standard-of-Care
Counts reflect numbers of adverse events. For EBV group, days calculated from most recent bronchoscopy. For Control group, days calculated from date of assessment procedure.

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Table E14: Summary of Changes in FEV_1, SGRQ, and 6MWD – EBV Subjects with Pneumothorax and No Pneumothorax (ITT Population)

	EBV Subjects with Pneumothorax (N=44)	EBV Subjects without Pneumothorax (N=84)
Post-Bronchodilator FEV_1 (L)		
Baseline	0.767 ± 0.269	0.762 ± 0.245
1-Year Absolute Change from Baseline	0.098 ± 0.221	0.105 ± 0.215
1-Year – Percent Change from Baseline	15.93 ± 28.03	17.64 ± 32.28
Responders ≥15% improvement	48.6%	47.3%
SGRQ Total Score (points)		
Baseline	55.80 ± 13.94	54.80 ± 14.24
1-Year Absolute Change from Baseline	-9.57 ± 15.53	-6.86 ± 17.56
Responders ≥4 points improved	57.3%	55.7%
Six-Minute Walk Distance (meters)		
Baseline	313.7 ± 83.6	310.1 ± 80.6
1-Year Absolute Change from Baseline	15.51 ± 85.36	11.12 ± 74.01
Responders ≥25m improved	37.8%	43.9%

Abbreviations: EBV, Zephyr Endobronchial Valve; FEV_1, Forced Expiratory Volume in 1 second; SGRQ, St. George's Respiratory Questionnaire; 6MWD Six-Minute Walk Distance.

Values are means ± SD